

(NASA-CR-160232) STUDY REPORT ON
INTERFACING MAJOR PHYSIOLOGICAL SUBSYSTEM
MODELS: AN APPROACH FOR DEVELOPING A
WHOLE-BODY ALGORITHM (General Electric Co.)
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STUDY REPORT
ON
INTERFACING MAJOR PHYSIOLOGICAL SUBSYSTEM
MODELS: AN APPROACH FOR DEVELOPING A
WHOLE BODY ALGORITHM

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PREPARED BY

D.G. Fitzjerrell
D.J. Grounds
J.I. Leonard, PH.D.

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1.0 BACKGROUND AND INTRODUCTION

Much of the work done under Contract NAS9-12932 was directed toward developing a whole-body algorithm as the culmination of this three-year research project. There were many benefits derived from the development of the building blocks of the whole-body algorithm which became end-items of significant value in themselves. In many cases, however, the end goal of a whole-body algorithm provided an important forcing function and focal point for this research without which many of these tools would not have been developed and refined to their present state.

The form of the whole-body algorithm at the end of this first version is probably somewhat different than was envisioned at the outset of this project because of a great deal of study and the advice of several consultants; many alternatives were considered before a workable approach to its development could be agreed upon. There were few guideposts because there had been few attempts, and indeed there have been few to date, to develop a model of this scope and magnitude.

Previous work has been done to couple subsystems and determine response but, with the exception of Guyton, the models were not integrated (interacting) or they were limited in scope, in the number of stresses, and in the degree of interaction between subsystems. For example, Smith and James (1964) produced a model for the heart rate of a man working in a hot environment. Atkins and Mitchell (1971) described thermal response of a working man. Albergone, et al (1972) and Womack and Hinderer (1971) described short term interactions between respiration and circulation. Friji-hara, et al (1973) described respiratory - circulatory interactions in exercise, and Farrell and Siegel (1973) modeled cardio-respiratory abnormalities. J. Mitchell, et al (1972) produced a model describing blood flow and oxygen uptake in muscles under exercise conditions.

Weissman (1971) developed a model for combined respiratory - thermo-regulation based on the models of Stolwijk and Grodins. Y. Fukui (1972) under the direction of Rideout and his group developed a beat-by-beat and breath-by-breath cardiovascular - respiratory model. These models of combined subsystems or of the interaction between subsystems are concerned with only two subsystems and many are concerned with only one stress response with various degrees of detail. Certainly any good model of only one subsystem must consider the effects from other body subsystems for most stresses in some, at least artificial, manner. A few investigators have considered up to three subsystems such as Walters (1973 and 1974) and Wissler (1973) have done for the cardiovascular, respiratory, and thermal subsystems. However, these models are again quite limited in scope and in stresses which they are capable of simulating, as in case of Walters' model and Wissler's model which are concerned only with the response to exercise in varied environmental conditions such as thermal and inspired gas concentrations.

Guyton (1972) has integrated the circulatory, fluid, and electrolyte regulatory subsystems with sufficient detail to be considered a tremendous step in the right direction. This model is capable of simulating the response of several subsystems to many and varied stress including many pathological states. The Guyton model with all its capability, however, has only a five-compartment non-pulsatile representation of the circulatory system and other shortcomings which make it inadequate for simulating many short term experiments of interest to this project such as Lower Body Negative Pressure (LBNP) and exercise experiments.

For a model to be considered a whole-body representation, it should at least be able to simulate the response of the major body subsystems to several stresses with reasonable accuracy at an acceptable level of detail for both short term and long term experiment simulations. The whole-body algorithm developed during this project and described in this report does have all these capabilities.

2.0 OBJECTIVES AND DESIGN APPROACH

The program objective, as stated in the program plan, is to develop a whole-body algorithm which will be useful for evaluating hypotheses related to physiological adaptation to space flight, developing new standards of remote medical care for advanced missions, and providing assistance to a real-time medical monitor during physiological testing. A whole-body algorithm which is capable of meeting this overall objective must be capable of simulating all of the important physiological functions of the major body subsystems. It must also be capable of simulating the primary interactions between these subsystems for various selected stresses. To be useful in evaluating hypotheses related to physiological adaptation to space flight, it must have the capability: (a) to simulate both the acute and long term changes in these systems, (b) to simulate the experiments used to evaluate this adaptation process, and (c) to simulate the environmental stresses which may influence the results of these experiments. The stresses of interest include bicycle ergometry (both supine and erect), LBNP, head-up tilt-table, passive standing tests, and environmental stresses of changes in cabin temperature and atmospheric composition (increased CO₂ concentration and hypoxia). The whole-body algorithm must, therefore, be designed such that the entire sequence of major physiological events for long duration space flight can be simulated. This includes the preflight (baseline or control) experiments, acute physiological response to zero-g, long term adaptation to zero-g, changes in cabin environment, inflight responses to the experiments of interest, acute reentry to 1-g, long duration readaptation to 1-g, and postflight experiment simulation. Since the individual subsystem and the integrated total body hypotheses for zero-g and return to 1-g have not yet been hypothesized and formulated, they cannot be modeled. The whole-body algorithm was, therefore, structured such that the capability to simulate this sequence of events exist.

After the zero-g hypotheses are derived, formulated, and tested, these mechanisms can be modeled directly into the whole-body algorithm. The whole-body algorithm could then be used to test the integrated total body hypothesis by direct comparison of the model output with the mission data. The verification of these design requirements will, therefore, be limited to 1-g experiment and environmental stress simulation. The long term physiological adaptation simulation capability will be tested by simulation of prolonged bed rest. The capability for simulating a typical space flight sequence will be tested by an analagous 1-g protocol. Thus, the physiological changes taking place during long duration space flight have been revealed in part by performing stress tests (such as LBNP and exercise) preflight, inflight, and postflight. An analogous 1-g sequence that will be simulated will consist of pre-bed rest short term stress tests (such as tilt-table and supine exercise), a long term bed rest, followed by the same short term stress simulations. These objectives and design requirements have been presented in detail in TIR 741-MED-4025 - Design Specification for the Whole-Body Algorithm.

The design approach is also discussed in detail in the Design Specification, but will also be outlined here because of its importance in this project. Several studies by various consultants preceded the selection of an approach and are discussed in TIR 741-MED-3058 - Study Report, The Development of a Whole-Body Algorithm, by Franklin J. Kay; TIR 741-MED-4018 - Research Report, Evaluation of Exercise-Respiratory System Modifications and Integration Schemes for Physiological Systems; TIR 741-MED-5001 - Research Report, Physiological Interactions with Emphasis on the Respiratory-Cardiovascular System, by R. R. Gallagher; and TIR 741-MED-4021 - Final Report, a Long Term Model of Circulation, by R. J. White.

There are probably two main approaches to modeling a large system composed of two or more major subsystems. First, each subsystem

could be modeled independently, possibly by different people using different hypotheses. After each subsystem has worked properly in some test situation(s), the subsystem models could be combined into a unit by restructuring or redesigning the subsystems to work together. Second, the system as a whole could be attacked and a cohesive model assembled utilizing a single non-contradictory set of hypotheses, and designed to function as a unit from the beginning as Guyton has done in his model. The basic approach to developing the whole-body algorithm was probably biased toward the first approach from the outset for two primary reasons. First, because individual subsystem models were developed from existing models or new models were developed under this program in order to be able to simulate the individual stresses of interest and to develop and test individual subsystem hypotheses related to physiological changes due to exposure to the space flight environment. Secondly, because of the difficulties encountered by Guyton and his co-workers in developing his model as well as those encountered in modifying the Guyton model for this program. These problem areas included, among others, considerations for various time lags, fast and slow controllers, changing integration step sizes, and disruption of the total model when modifications are made.

Coupling of existing subsystem models offers the advantage of having each model already capable of simulating each stress of interest individually in a stand-alone mode. Each model can then also consider various time lags, fast and slow controllers, and integration step sizes as appropriate for their respective simulation requirements. This approach also provides the versatility required such that modifications can be performed without total disruption of the system. The model needs to change as more experimental data are available, new information is gained from the literature, new hypotheses are verified, or as

results from the simulations indicate an inappropriate formulation has been made. For these reasons, the basic approach of combining individual subsystem models in some physiologically meaningful way was selected for developing a whole-body algorithm.

The individual subsystem models, as has already been mentioned, were developed or modified from existing models to be capable of simulating the stresses of interest on the same computer system and in the same language. These models and the various modifications have been described in detail in the literature and in previous TIR's and, therefore, will not be repeated here. The Guyton model (Guyton, 1972); with modifications by White is documented in TIR's - 741-MED-3042, 4017, and 4021, is capable of simulating intermediate and long term changes in circulatory, fluid and electrolyte control. The respiratory subsystem is represented by Grodins' model (Grodins, 1967) with modifications by Gallagher in TIR's - 741-MED-3047, 4016, 4018, and 5001. The Stolwijk thermoregulatory subsystem model (Stolwijk, 1970) with modifications by GE is described in TIR's - 741-MED-3013, 4011, and 4014. The cardiovascular subsystem is represented by a model developed under this contract by Croston for Bicycle ergometry exercise (Croston, 1973) with modifications by Fitzjerrell and Croston for LBNP, tilt, and tilt (supine) ergometry and is documented in TIR's - 741-MED-2010, 3053, 3054, and 4008.

The basic compatibility of these subsystem models seems evident since they are all represented by a controlled system or plant and a controlling system or controller which functions normally as a negative feedback control system. The technical plan for accomplishing the integration of these subsystem models included:

1. Verifying the subsystem modeling approach
2. Verifying the compatibility of each subsystem model
3. Providing for system expansion

4. Unifying the system software programs, languages, and the subsystem computational approach.
5. Controlling interfaces (i. e., inputs, outputs, and subsystem interfaces)
6. Providing uniform experimental checkout of each subsystem and the assembled algorithm
7. Examining all interfacing closed-loops for stability
8. Developing the whole-body executive program to control execution of the subsystems
9. Whole-body algorithm validation

This plan leads to a whole-body algorithm that is limited only by the detail of the individual subsystem models, the lack of physiological experiment data to further refine the models, and the lack of knowledge of certain physiological phenomena. Such a model provides a basis for studying physiological phenomena and a basic model which can be refined as new parameters are recognized or needed.

Although this discussion may indicate that the task would be easy, any such idea will quickly be dispelled by simply considering any two of the subsystem models. All of these subsystems were developed with different goals in mind; each model assumes or calculates common parameters using different approaches; and each model was developed to obtain certain responses to specific experimental stresses. To further complicate model interfacing, baseline data such as blood volumes, basal or resting metabolism, control systems, units, variable names, volume compartmentization, integration schemes, and programming approaches all differ considerably in the various subsystem models. These details can only be worked out directly at the program level, so the details of this basic approach can only be worked out by total commitment to the task and many manhours of work.

One point that is evident for this approach from the outset is that the Guyton model with some modification is capable of simulating the long term adaptive changes in the major body systems such as fluid volume shifts and electrolyte changes. The response of this simulation could then be used to automatically define initial operating conditions for the short term models. The short term models could then simulate any short term stresses (such as exercise or LBNP) or transient changes in environmental conditions, after a new steady-state was reached, and could reinitialize the long term model for the next long term phase of the simulation. The problems involved in accomplishing this type of bilateral interface are related to the non-uniqueness of the transition between the models, and the fact that the controlling systems for the short term models should be initialized also. How can arterio-venous muscle blood flow from a five-compartment model be used to initialize a 28-compartment model? The only reasonable approach appears to be that such degrees of freedom must be chosen to correspond to known physiological conditions in the subject at the time the short term to long term interaction takes place.

The interactions between the three short term subsystem models (cardiovascular, respiratory, and thermoregulatory) is quite a different problem. To provide a representation of the response of the other subsystems to a stress applied to any one of them, these models must operate simultaneously (or very nearly so) in time with the values of the interfacing parameters updated automatically and made available when needed by the other subsystem computations as simulation time progresses. Since each of the short term models have different integration step sizes, the only approach which seemed feasible was to step each model ahead in time until its calculated time exceeded simulated time, alternating between calculations in each model, and advancing each in a step-by-step

rotation until the short term simulation time is reached. A complicating factor which presented itself in this procedure was that all of the short term subsystem models will not fit in core at the same time. It was, therefore, necessary to rotate the models in and out of core taking care not to lose the present calculated values of the parameters used not only in the interface between models, but internally as well. This "overlaying" procedure requires that all variables be defined in a common area that remains in core during the simulation.

It is impossible to face all the modeling problems that one must solve to construct the whole-body algorithm without actually implementing the model. Design and implementation are so intertwined in a model of this size that it is actually inefficient to try to develop specific detailed approaches until implementation. For this reason, much more attention was given to alternative general approaches prior to actual implementation without much concern for how these details could be worked out. The next section deals with the approach to and the resolution of these details as they were implemented for the selected general approach.

3.0 DESIGN AND DEVELOPMENT

The design of the Whole-Body Algorithm provides for the simulation of both long and short term stresses. The long term simulation is accomplished by a circulatory, fluid and electrolyte subsystems model which then initializes a set of three short term models representing the cardiovascular, respiratory, and thermoregulatory systems. These three short term models, which are designed to simulate the responses to acute changes in environment and short term experiment stresses, operate in parallel fashion interchanging information as often as every half second of simulation time. Using this approach, a Whole-Body Algorithm evolved which could simulate with equal facility those adaptive changes which require days, weeks, or even months of simulation time, as well as those experimental stresses in which significant changes might occur in a matter of seconds.

3.1 LONG TERM FLUID AND ELECTROLYTE SUBSYSTEM

The individual subsystem models which were utilized for this project were carefully selected and modified to simulate the response of a human subject to the stresses under investigation in the Skylab medical experiments. The long term model of circulatory, fluid and electrolyte control, which was originally developed by Guyton (1972) has been substantially modified to include the most current formulations for many of the regulatory functions and implemented in an interactive time-sharing mode. The documentation of these changes is described in Section 2.0.

The systems analysis of overall circulatory regulation as developed by Guyton considers a large number of the physiological subsystems that affect the circulatory system. This model consists of 354 blocks. Each block represents one or more mathematical functions that describe

some physiological facet of circulatory regulation. The model illustrated in Figure 3-1 is based on cumulative knowledge of the circulation and on experimental data.

The circuit of the blood flow in the Guyton model is divided into five volume segments: the aorta, the veins, the right atrium, the pulmonary arteries, and the combination of pulmonary veins and left atrium. The Guyton model includes fluid and electrolyte balance as part of the system. Also included in this model are representations for ventricular muscle strength, hypertrophy of the heart, deterioration of the heart, and autonomic and sympathetic stimulation. These factors enable the simulation user to calculate the effect of changes in these parameters on circulation. The inclusion of such parameters as cardiac hypertrophy, cardiac deterioration, etc., clearly indicate that the Guyton model was developed to be useful as a long term model. This feature makes it very attractive as a companion to a short term pulsatile cardiovascular model for the whole-body algorithm application.

Many and varied experiments can be simulated with the Guyton model including infusions of water electrolytes and plasma, congestive heart failure, loss of kidney function, nephrotic proteinuria, and angiotension infusions. However, the long term simulation chosen for the whole-body algorithm was bed rest because it has long been considered as an analog to zero-g. Although the model is basically capable of simulating this stress, it was not initially designed to do so and some modifications to the model were required to properly simulate this stress which will be discussed in detail in Section 4.0.

3.2 CARDIOVASCULAR SUBSYSTEM

A model of the human cardiovascular system and its controls was developed under this contract by Croston to simulate bicycle ergometry exercise. Subsequent modifications to this model by Fitzjerrell and

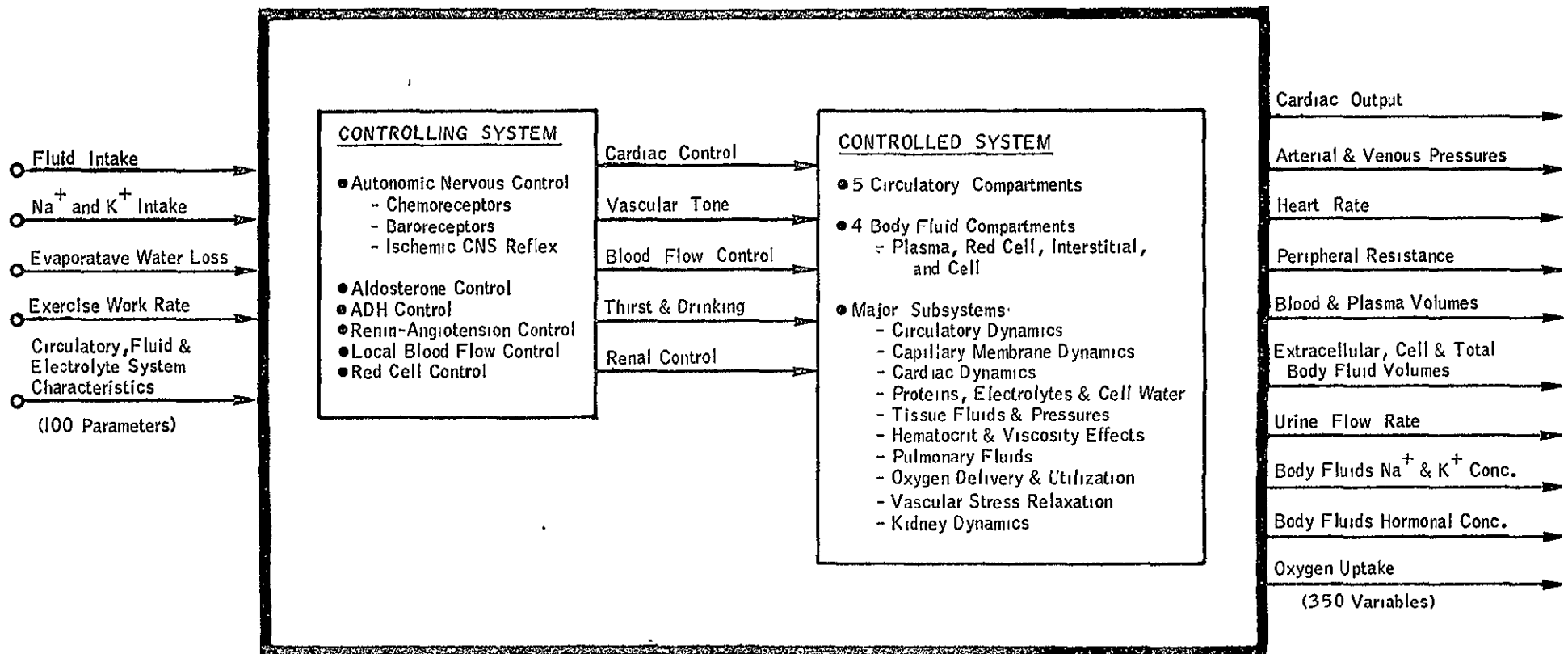


FIGURE 3-1 CIRCULATORY DYNAMICS, FLUID AND ELECTROLYTE BALANCE MODEL

Croston were made to enhance the design for simulation of LBNP, tilt, and tilt ergometry. The Croston model includes gravity effects, muscle pumping, venous tone, venous valves, respiratory frequency, and intra-thoracic pressure effects. Complex cardiovascular control hypotheses are modeled for the control of the heart period, peripheral flow resistances, venous tone, and other controlled variables. Metabolic control mechanisms are modeled by mathematical representations of oxygen uptake, oxygen deficit, and accumulating metabolites to simulate a transient metabolic state.

The cardiovascular circulatory system is broken into 28 compartments to describe pulsatile blood flows, pressures, and volumes. This model of the circulatory system is combined with formulations of the controlling systems shown in Figure 3-2 to simulate transient responses to exercise. Command inputs to the model are assumed to be from chemoreceptors, neurogenic inputs from muscular activity, and neurogenic anticipation. Other inputs needed are the exercise workload, work rate, gravity, oxygen requirement for rest and cardiac output. Typical outputs which can be selected are oxygen uptake, oxygen deficit, total metabolites, heart rate, various blood flows, systolic pressure, mean pressure, diastolic pressure, stroke volume, venous pressures, and arterial pressures. The control system section was subsequently modified to develop a new model to simulate lower body negative pressure (LBNP) and tilt experiments.

3.3 RESPIRATORY SUBSYSTEM

The respiratory system model of Grodins was selected for use in the development of the whole-body algorithm. Grodins' model is also represented as closed-loop control as illustrated in Figure 3-3. Grodins has divided the controlled system into three compartments

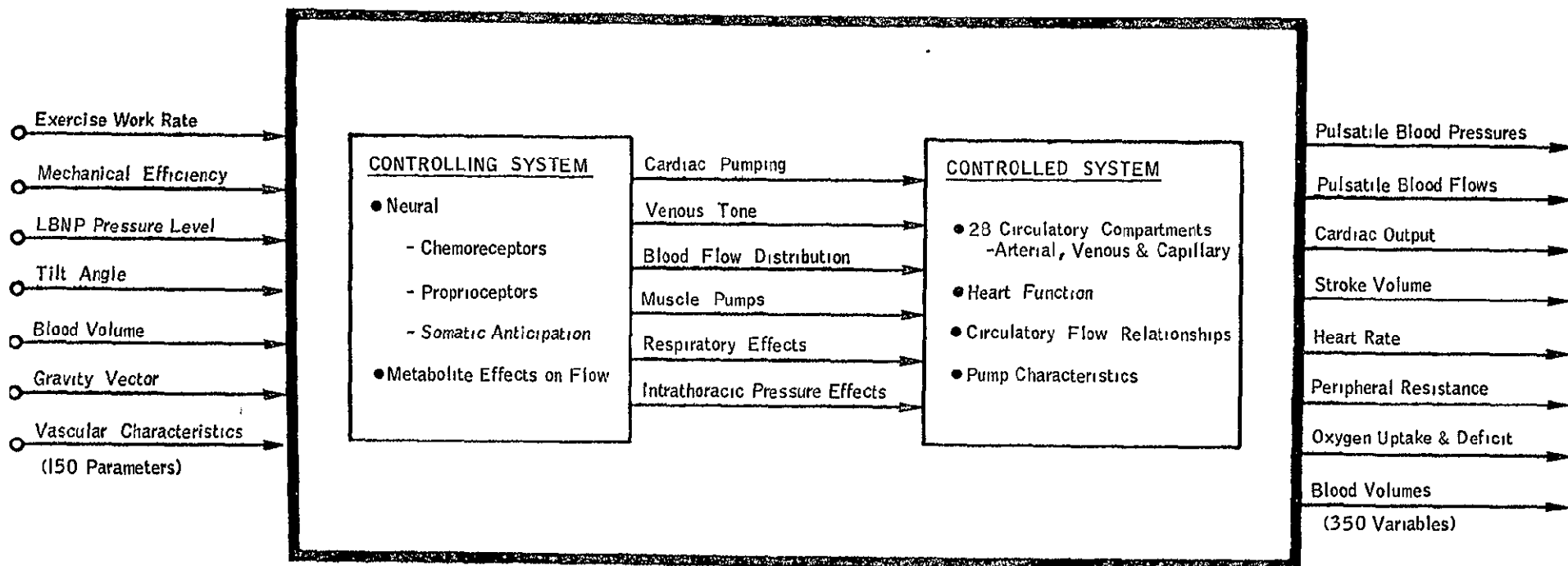


FIGURE 3-2 PULSATILE CARDIOVASCULAR MODEL

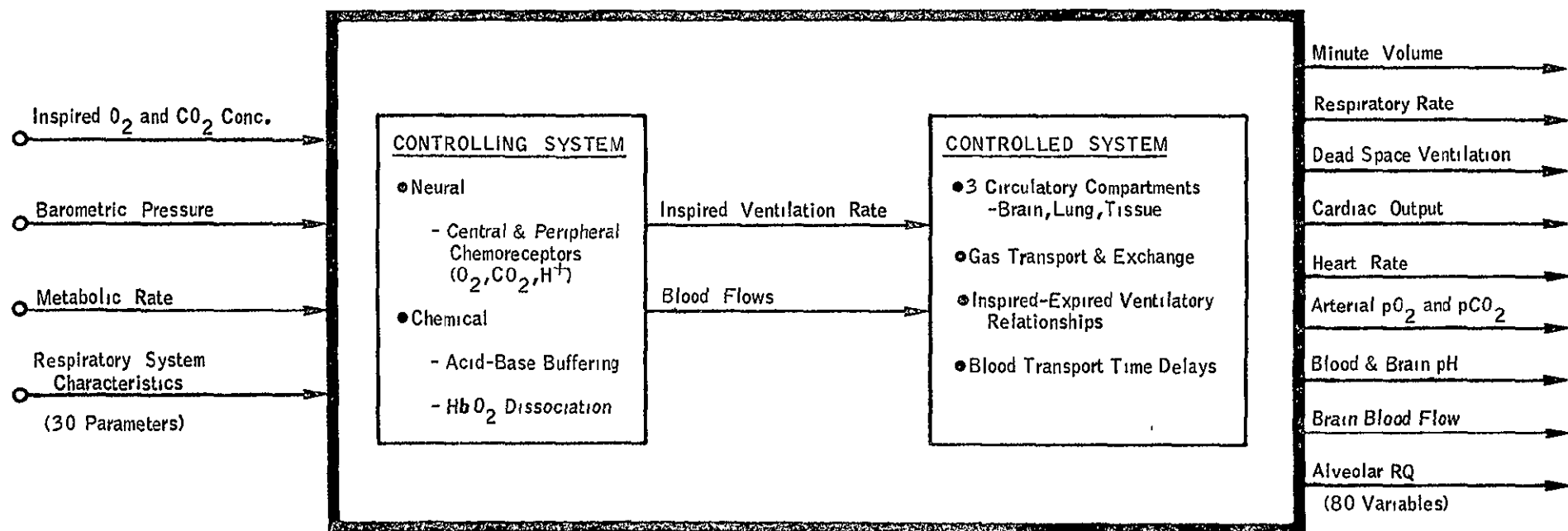


FIGURE 3-3 RESPIRATORY SYSTEM MODEL

(lung, brain, and tissue) as shown in the figure. The lungs are treated as a box of constant volume, uniform content, and zero dead space ventilated by a continuous unidirectional stream of gas. If the alveolar respiratory quotient differs from unity, the rates of inspired and expired gas will differ.

The blood passes through the lungs and after a transport delay that is dependent on vascular volume and blood flow rate, the arterial blood arrives at the brain or the tissue compartment. In this model, CO_2 and O_2 exchange rates are governed by metabolism.

The brain compartment communicates with the cerebrospinal fluid reservoir via a membrane permeable to respiratory gases only. The diffusion rates across the membrane are proportional to their tension gradients. Venous blood exiting the brain combines with venous blood from the tissue after a time delay forming mixed venous blood. After another delay this mixed venous blood enters the lungs to complete the cycle of gas transport and exchange. Total cardiac output and local blood flow have been found to vary as functions of arterial CO_2 and O_2 tensions, however, Guyton's circulatory model control utilizes only O_2 tensions.

The real system is composed of receptor elements which monitor chemical concentrations, afferent nerves which transmit this information to the central nervous system, neural centers, and motor nerves to the respiratory muscles which drive the thorax-lung pump. In the model of this system, this process is represented by chemical concentrations at receptor sites as inputs to the system and ventilation as the output.

3.4 THERMOREGULATORY SUBSYSTEM

A dynamic model of physiological regulation of body temperature in man has been developed by Stolwijk and modified by General Electric

and others. The thermoregulatory system is modeled as a control system and a controlled system. The controlled system is the mathematical representation of the thermal characteristics of the various geometric compartments of the body. Thermal loads act on the controlled system and cause a response that may be considered as a variation from homeostasis. Sensor mechanisms, as part of the control system, feel these changes and induce corrective action to reduce or control the effect of the loading within acceptable limits.

A total of 41 nodes is used to represent the thermal characteristics of the body with four nodes each representing the head, trunk, arms, hands, legs, and feet. The forty-first node represents the central blood compartment. The four nodes representing each of the segments are composed of concentric layers treated as core, muscle, fat, and skin. Each node has the appropriate metabolic heat production, convective heat exchange with adjacent compartments. The nodes representing the skin exchange heat with the environment via radiation, convection, and evaporation.

The thermoregulatory model receives temperature signals from all compartments and, after integration and processing, the control system causes appropriate commands to be sent to all appropriate compartments changing metabolic heat production, blood flow, distribution, or the rate of sweat secretion. A schematic of the system is shown in Figure 3-4.

The thermoregulatory system presented is basically concerned with the effects of external temperature (environment) and the effects of metabolic heat production (exercise). The controlling system is developed to maintain a heat balance utilizing all facets of heat transfer. Control equations consist of the product of a control coefficient and a central temperature signal, the product of a control coefficient and an integrated skin temperature signal, and a third term consisting of a control coefficient, a central temperature signal, and skin temperature

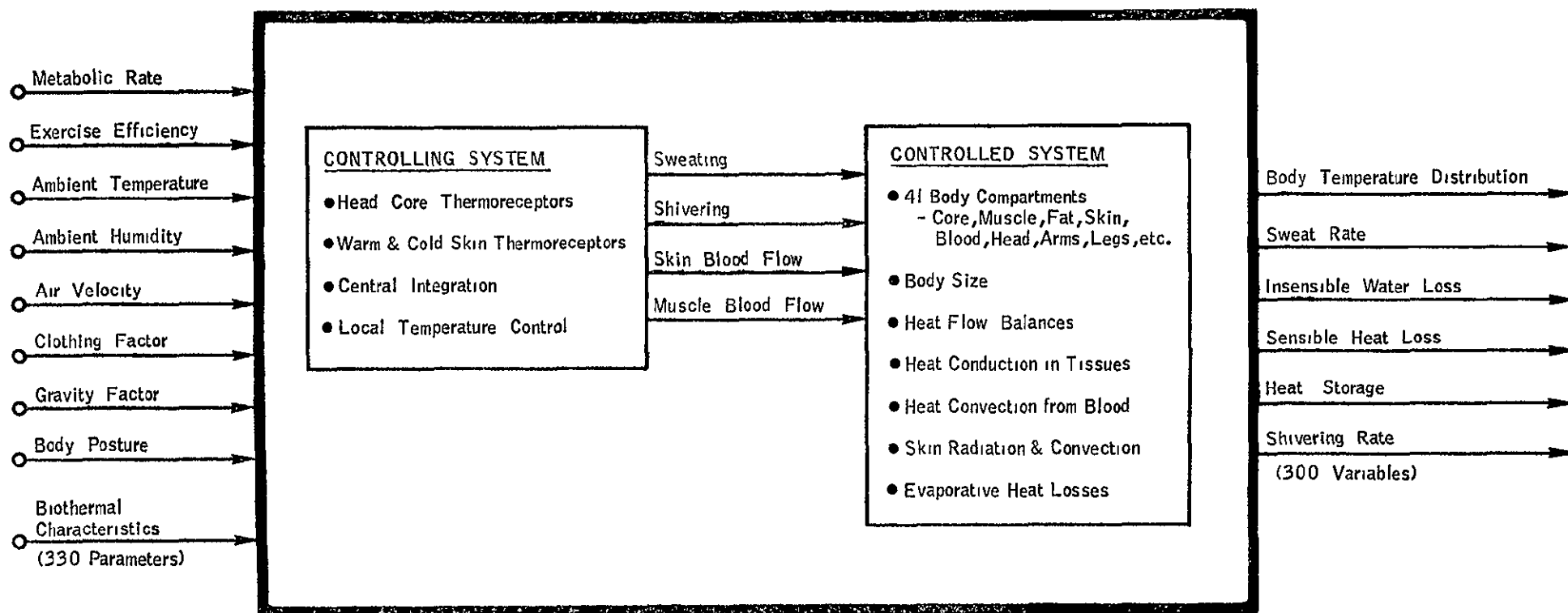
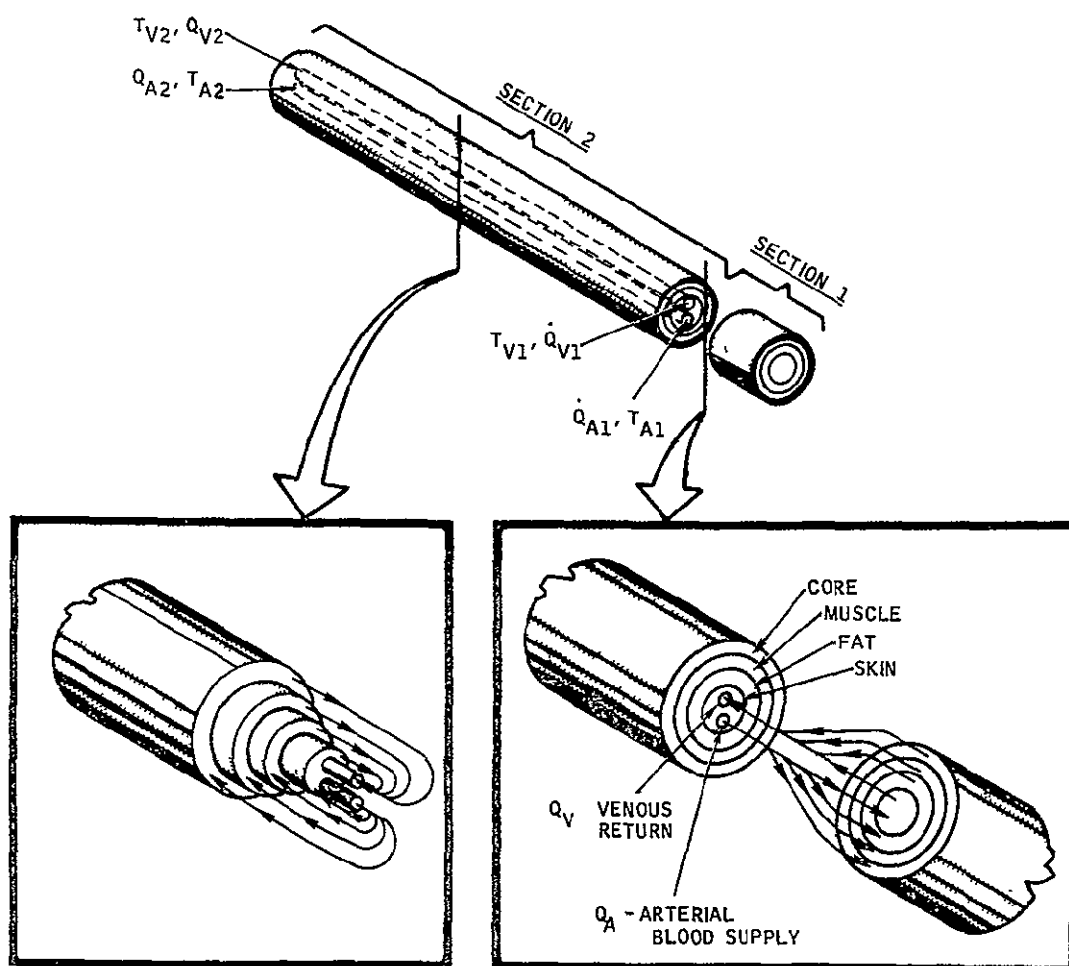


FIGURE 3-4 THERMOREGULATORY SYSTEM MODEL



$$\dot{Q}_{V2} = \dot{Q}_{A2}$$

$$\dot{Q}_{V1} = \dot{Q}_{A1}$$

$$T_{V1} = \frac{\sum_{i=1}^4 (BF_{i1} * T_{i1})}{\dot{Q}_{A1}}$$

$$T_{V2} = \frac{\sum_{i=1}^4 (BF_{i2} * T_{i2})}{\dot{Q}_{A2} - \dot{Q}_{A1}}$$

$$CCH = (T_{V1} - T_{C1}) * \dot{Q}_{V1} + (T_{V2} - T_{C1}) * (\dot{Q}_{A2} - \dot{Q}_{A1}) + (T_{A2} - T_{C1}) * \dot{Q}_{A2}$$

ALL VARIABLES ARE KNOWN EXCEPT THOSE ON THE L.H.S. OF THE EQUATIONS

\dot{Q}_{V2} = BLOOD FLOW RATE (VENOUS RETURN, SECTION 2)

T_{V1} = TEMPERATURE BLOOD (VENOUS RETURN, SECTION 1)

T_{C1} = TEMPERATURE OF CORE COMPARTMENT OF SECTION 1

CCH = TOTAL COUNTERCURRENT HEAT EXCHANGE

FIGURE 3-5 COUNTERCURRENT HEAT EXCHANGE

signal. These control equations affect the temperature change by controlling skin blood flow, causing a sweating response, or instigating the muscular activity of shivering.

This model is based on a man with a body weight of 74.1 Kg and a surface area of 1.89 m^2 . Inputs to the system are thermal properties, geometric or volume parameters, basal conditions, environmental conditions, and time or duration of exposure.

Modifications to the basic thermoregulatory model were required for its use in the whole-body algorithm. The increase in metabolic rate from a basal to a resting state, as required by the design approach, was seen in the thermoregulatory model as mild exercise. Since metabolic heat generated during bicycle ergometry is distributed heavily to the leg muscles, adjustments were made to distribute the resting metabolic heat more equitably to other muscle compartments by muscle mass. The second area, which will be documented more completely in a forthcoming Technical Information Release (TIR), was the addition of countercurrent heat exchange to the model's blood supply to improve model performance in a cool environment. The changes as illustrated in Figure 3-5, represent the blood compartment as being in intimate thermal contact with the core compartments of the trunk, arms, and legs and with returning venous blood. These mechanisms become increasingly important in a cooler environment, as the venous return from muscle and skin are significantly cooler than the arterial blood supply which both pass through core segments.

3.5 SUBSYSTEM INTERFACES

The individual models have been described in the form in which they were used in the whole-body algorithm. This section describes the interfaces which were developed to represent the proper interaction between these subsystems. A diagram illustrating these interfaces is presented in Figure 3-6 where the variables are defined as shown.

The general philosophy was to integrate the various models in a manner which causes the least number of modifications to the basic model formulations, even at an occasional loss of computing efficiency. Since the units used in each of the models were substantially different, there was frequently a need to convert the units of variables passed between models. The rule for the Whole-Body Algorithm was that conversion factors would be applied on the receiving end of the transfer where necessary. The task of converting all the models to a single set of consistent units is being relegated to a recommendation for future work.

Long Term - Short Term Interface

This interface, as shown in Figure 3-6, while technically the least difficult to accomplish, provides one of the most important physiological relationships in the whole-body algorithm for providing the capability to simulate the space flight event sequence. From the modeling viewpoint, the basic plan was to use the long term model to initialize the short term models to simulate any short term experiments or transient environmental conditions which would then, after steady-state conditions were reached, initialize the long term model for simulation of the subsequent long term phase. Since the long term - short term interchange under this plan is sequential rather than simultaneous, the modeling problem was primarily one of providing for the transfer of the interface variables through a common block and modeling the mechanisms necessary to use these variables on either side of the interface in a physiologically representative manner.

The major problem areas encountered, then, were more related to the choice of variables to be passed through the interface and to the problem of simulating a physiological state which could be represented in both the long term and short term models at the time of transfer. A

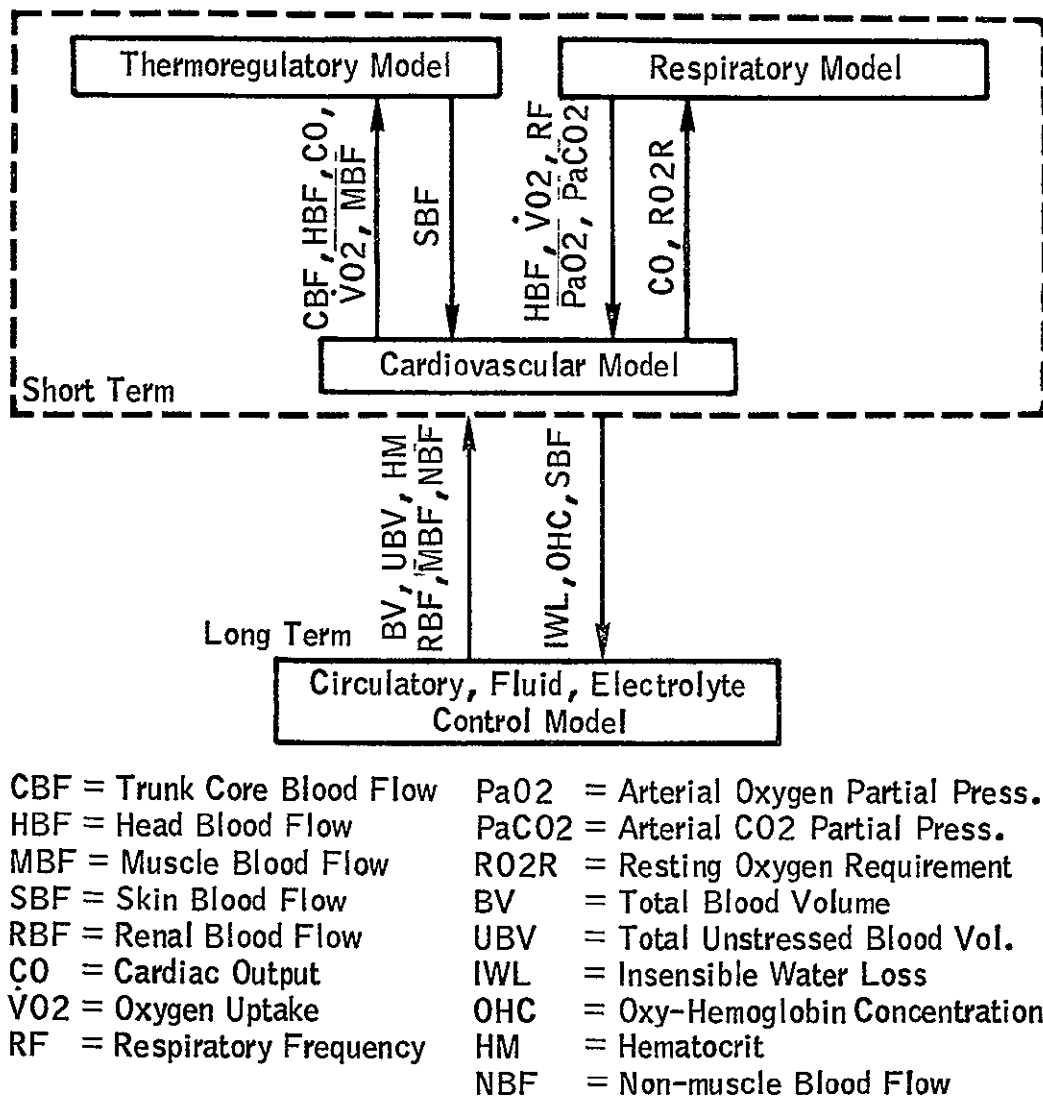


FIGURE 3-6 SUBSYSTEM INTERFACES

supine resting (but not basal) state was decided upon since this condition best represents the state that exists just prior to beginning any short term stress and is closely related to the passive zero-g state. To properly represent this state in all the subsystem models at the time of transfer required that they be initialized to this state. This was accomplished by matching metabolic rates (equivalent to the resting supine oxygen uptake), initial blood volumes, and major blood flows in all the models. However, since the environmental conditions could change to a new state and remain at that state for an extended period of time, the long term - short term interface must include the capability to reinitialize the long term model to this new resting supine state after the transient was simulated in the short term models and a new steady-state has been reached. These variables are insensible water loss, oxyhemoglobin concentration, and skin blood flow. This design also provides the structure for simulating the space flight sequence except for the postflight condition whereby long term adaptation to 1-g simulation may be required. Since the long term model does not have the capability to simulate postural changes in the gravity field, some model changes would be required if this condition were to be simulated.

The next problem, which was to select the variables to be passed through the interface other than those required to represent changes in the supine resting state for environmental changes, is a direct function of the long term stresses to be simulated and the resultant hypotheses related to the physiological representation of these stresses. The short term experimental stresses (other than environmental) should not impose any interface requirement to the long term model since it is assumed that the short term experiment simulation would always include recovery back to the same initialized state that existed prior to the stress and that no long term physiological state changes would result from the performance of the short term experiment. If this assumption was found not to be correct, some new variables would have to be added to the interface.

Bed rest was the long term experiment of choice to be simulated since this experiment has long been considered to be an analog of long duration exposure to zero-g. The primary physiological response to this experiment which would affect the initial state of the short term models (and, therefore, must be passed through the interface) is associated with the headward redistribution of blood and the resultant changes in blood volume, vasomotor conditions, hematocrit (due to plasma filtration), and blood flow through the major flow paths. Changes in total blood volume and total unstressed blood volume provide the necessary information to the short term models for initializing blood volume and vasomotor changes (except changes in tone which was not considered in the bed rest hypothesis). Hematocrit is passed through the interface to provide the respiratory subsystem effect due to changes in red cell concentration. The blood flow changes in the renal, muscle, and non-muscle paths of the long term model are passed through the interface to provide flow changes in the major flow paths of the cardiovascular models. These flow changes were converted to a corresponding resistance change and applied to the respective flow paths represented in the cardiovascular model. The renal blood flow change was represented by a resistance change in the renal arterioles, the muscle blood flow change was represented by a resistance change in the leg arterioles, and the non-muscle blood flow change was represented by a change in the resistance of the superior mesenteric artery. These hemodynamic changes are then reflected in the respiratory and thermoregulatory subsystems through the flow parameters in their respective interfaces with the cardiovascular subsystem during the simultaneous operation of these short term models.

The other model changes, other than those required to accommodate the variables passed through the interface as discussed above, are associated with the specific hypotheses for physiological changes during bed rest. These changes as well as the requirements for additional

variables to be passed through the interface to represent these hypotheses will change as different hypotheses are considered. One value of the design approach selected for the whole-body algorithm is realized in this area when these changes can be made with relative ease to test alternate hypotheses without total disruption of the entire system.

These hypotheses and the required model changes are discussed in detail in Section 4.0. The modeling of the hypotheses dealing with long term heart rate changes and reverse stress relaxation occurring during bed rest have been left in the whole-body algorithm formulation and should be considered when repeating the simulation of bed rest with additional or different hypotheses.

It should be noted that this interface, and for that matter all the interfaces between all the subsystems, were designed for the simulation of the 1-g response to the stresses of interest with the hypothesized physiological changes and responses as documented in this report. The assumption of different conditions, other stresses, different or additional hypotheses, or combinations of stresses (multiple or sequential) would require additional or different variables to pass through the interfaces and new modeling to accommodate the passed variables in the receiving subsystem models as well as modeling the mechanisms of the hypotheses as they are manifest in each subsystem. The whole-body algorithm has been designed, however, to accomplish this with relative ease.

Cardiovascular - Respiratory Interface

The interface between these two subsystems presented the most difficulty and, therefore, received more attention. This is probably, in part, due to the physiological interaction and interdependence of these two subsystems. It may also be because a larger number of short term stresses of interest to this project have responses manifested in these subsystems.

The first problem encountered in interacting these two models was that the initialized (resting) metabolic rate was different in each of the models. This was a problem, in fact, that was encountered in all the model interfaces. The initial metabolic rate in the cardiovascular model is represented as a resting (non-exercising) oxygen uptake for an alert and ready subject. The other models had the metabolic rate initialized much more closely to a basal rate. The initial attempt to solve this problem was to pass the resting oxygen requirement from the cardiovascular model to the other models. This resulted in the other models responding as if a very low level of exercise were commanded and, in the case of the respiratory model, ventilation was driven to a level commanded by the higher oxygen uptake above its initialized level. This response, of course, did not effect the exercise response, but did cause an improper response of the respiratory model to other stresses such as increased CO_2 inhalation, hypoxia, tilt and LBNP experiment simulations which in turn effected the cardiovascular response to these stresses through the interface variables. All the other models, then, had to be reinitialized to a resting metabolic rate equal to that in the cardiovascular model for a supine unstressed representation. The resting oxygen requirement still had to be passed from the cardiovascular model in order to get the other models to respond to the passive (non-exercising) changes in resting oxygen requirement such as that which occurs when the upright position is assumed.

The other interface variables were chosen to represent those which changed significantly during the stresses of interest and would have a significant effect on the response of the subsystem model on the other side of the interface. The direction in which these variables were passed was decided based on which model had the better physiological representation relating to the variable of interest. In most cases, this selection was quite easy since the counterpart representation of the

interfaced model subsystem was generally represented in an entirely artificial or empirical fashion in the other subsystem model (e.g., respiration in the cardiovascular model was represented by an external pressure on the thoracic blood compartments). In some cases, however, new formulation had to be added to the receiving model in order to get it to respond properly to the passed variable since, in many cases, the receiving model had not been designed to respond to stresses generated in the sending model. This was true for cardiovascular response to environmental stresses such as changes in inspired gas concentrations where chemoreceptors sensitive to changes to arterial partial pressures of oxygen and carbon dioxide had to be modeled.

The chemoreceptor reflex was modeled in the cardiovascular model to be sensitive to increases in CO_2 and decreases in O_2 in much the same way that the baroreceptors respond to changes in blood pressure. The basic control idea was derived from Scher (1974) as shown in Figure 3-7. The basic equation derived to produce the chemoreceptor autonomic reflex is:

$$\text{AUNC} = 1.0 + (0.03448 \text{ DPCO}_2 - 0.016 \text{ DPO}_2)$$

where AUNC is chemoreceptor autonomic effect and DPCO₂ and DPO₂ are changes in arterial CO₂ and O₂ partial pressures, respectively. This autonomic factor was then applied to the calculations for peripheral resistances, heart rate, and strength of heart contractions in the manner depicted in Figure 3-7. These changes then change blood pressure (which feeds back to the baroreceptors which also effect the calculations mentioned above), stroke volume, and cardiac output which is passed to the respiratory subsystem model completing the feedback loop across the interface. It was also found to be necessary to limit the effect of the changes in PaCO₂ and PaO₂ based on information from Duffin (1971)

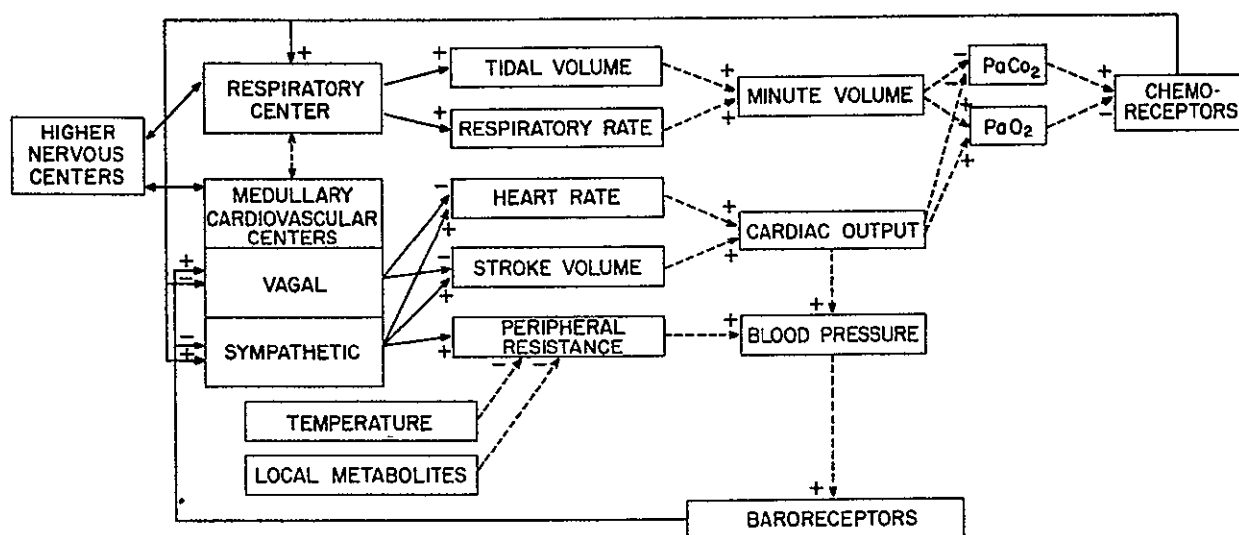


FIGURE 3-7 BLOCK DIAGRAM OF AUTONOMIC CONTROL SYSTEM

A summary of the major components of the cardiovascular and respiratory control systems. A plus sign indicates that an increase in the input into one of the components increases its output. Thus, when the pressure rises at the baroreceptor the sensory nerves will increase firing, and there will be a decreased firing in sympathetic fibers with an increased firing in the vagal fibers. This will produce a vasodilation, decreased heart rate, decreased stroke volume, and a fall in peripheral resistance. The changes in heart rate and stroke volume will decrease the cardiac output which, combined with the fall in resistance, will decrease the blood pressure which, in turn, will decrease the pressure at the baroreceptors.

An increase in CO_2 or decrease in O_2 at the chemoreceptors will increase the sensory discharge causing a decreased vagal and increased sympathetic activity. This will result in increased heart rate, increased stroke volume and increased peripheral resistance. The heart rate and stroke volume changes produce an increase in cardiac output which, combined with the increased peripheral resistance, increases the blood pressure. In addition, there will be respiratory effects increasing the respiratory minute volume, and these two factors should result in increased carriage of O_2 to the tissues.

in which studies were presented which showed the response of the carotid chemoreceptor to be very low or zero for PaO_2 greater than 80 mm Hg and PaCO_2 less than 30 mm Hg.

The next major problem area encountered in interacting these subsystems was in the response to exercise. It was noted, after all the interface links were established, that very good response from both subsystems was elicited for high exercise levels (150 to 200 watts), but poor response (worse than that for the stand-alone models) for the lower levels (100 watts and below). This problem was traced to the rate of oxygen uptake from the respiratory subsystem model being significantly different for the lower exercise levels than that which was generated in the cardiovascular model in a stand-alone mode even though the steady-state values were the same. This caused a significantly different response from the cardiovascular subsystem model since the oxygen uptake is integrated (i. e., the area to the left of the oxygen uptake curve) to calculate oxygen deficit. The different oxygen deficit caused a very different response because this variable effects many control functions in the cardiovascular model. After careful study of the representation of oxygen uptake functions in the respiratory subsystem model, it was noted that, while different exponential functions were generated with different time constraints as a function of exercise level, only one exponential function is used to represent the oxygen uptake curve for any one exercise level. The studies of Whipp and Wasserman (1972) indicate that oxygen uptake curves for exercise levels greater than 100 watts cannot be represented accurately by a single exponential function. This information would seem to indicate that the model's response should have been poor at the higher levels of exercise and good at the lower levels instead of the reverse. This discrepancy was resolved when the oxygen uptake curve from the respiratory subsystem model was compared with the data from this source for 200 watts and found to provide

a very similar oxygen deficit in spite of a poor curve fit. The curve had an undershoot on the low end and an overshoot at the high end resulting in very close to the same area to the left of the curve. When this same exponential function (which was probably tuned for the high exercise levels because of the greater chance for error at the high levels) was applied for the lower exercise levels, the curve had a significant overshoot to the same steady-state level as compared to the data. This problem was resolved by deriving a multiple exponential function for the higher exercise levels and a single one for less than 100 watts based on the data from Whipp and Wasserman. These new oxygen uptake functions programmed in the respiratory subsystem model are shown in Figure 3-8 for 100 and 200 watts. Note that the curve for 200 watts, which is represented by a multiple exponential function, breaks at approximately two minutes into the exercise as was indicated by the experimental data. This break corresponds to the anaerobic threshold which is also indicated by the experimental data (see Figure 3-9). When the exponential function (rate of change of oxygen uptake, $\dot{V}O_2$) is plotted on a semilog scale, it becomes a straight line whose slope is the time constant. As can be seen from this plot, each exercise level requires not only a different time constant, but a minimum of two exponentials are required to represent oxygen uptake rates for exercise levels greater than 100 watts. The curves for this subject also show the break (anaerobic threshold) to be very near the two minute mark into the exercise for all the levels above 100 watts. After these new oxygen uptake functions were modeled in the respiratory subsystem model, the oxygen deficit function in the cardiovascular model was tuned for this data and good response from both subsystems were elicited for all levels of exercise (see Section 4.0).

Cardiovascular - Thermoregulatory Interface

The principal functions of the thermoregulatory subsystem are to simulate changes caused by variations in environmental parameters

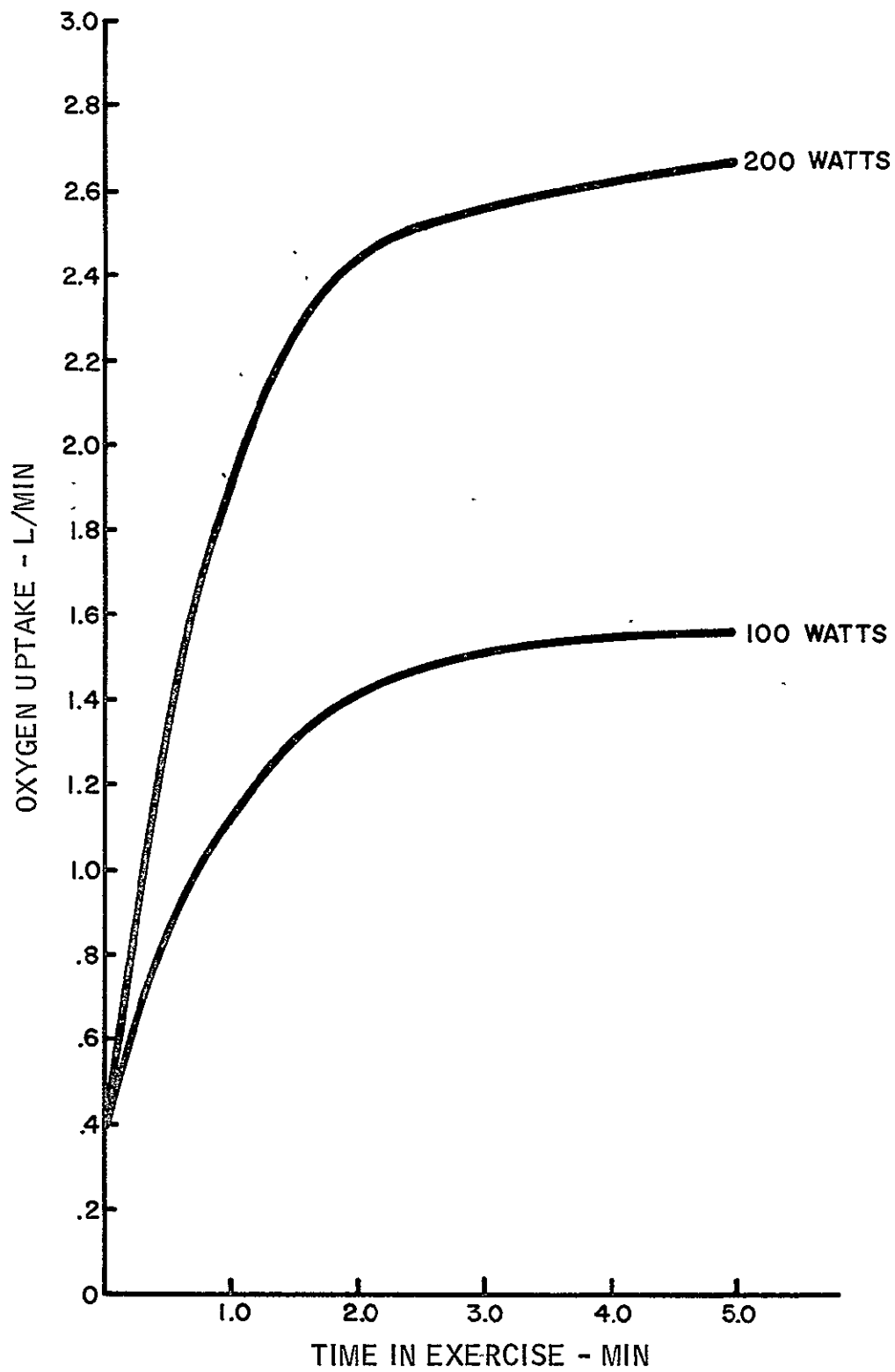


FIGURE 3-8 NEW OXYGEN UPTAKE FUNCTIONS MODELED IN THE RESPIRATORY SUBSYSTEM

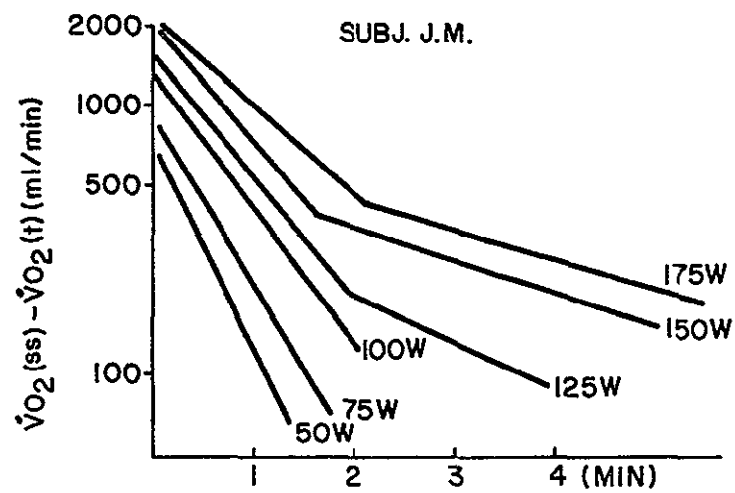


FIGURE 3-9 RATE OF CHANGE IN OXYGEN UPTAKE, $\dot{V}O_2$ AS A FUNCTION OF TIME IN EXERCISE FROM WHIPP AND WASSERMAN (1972)

(e.g., temperature, relative humidity, barometric pressure, cabin ventilation, clothing, etc.) and increases in metabolic production of heat (exercise). The function of the cardiovascular system, in the context of thermoregulation, is to provide a fluid medium for convective heat transfer away from tissues which are warmer than the blood and into tissues which are at a lower temperature than the blood.

The blood supply to the skin is of great interest to both cardiovascular and thermoregulatory subsystems. The skin is a principal source of heat exchange with the environment through the pathways of radiation and convection. The amount of heat exchanged through these pathways are functions of the temperature of the skin and the various environmental factors mentioned above. The temperature of the skin is determined through a heat balance of these environmental heat exchanges, through conduction to the adjacent fat compartment and convective heat exchange with the blood supply. The temperature of the skin acts in a feedback loop in the thermoregulatory subsystem to control the production of sweat and the skin blood flow through the mechanisms of vasoconstriction and vasodilation. Therefore, since the skin blood flow is largely a function of the state of thermoregulation, the value for this parameter is computed and passed from the thermoregulatory subsystem to the cardiovascular subsystem. The other parameter being passed from the thermoregulatory to the cardiovascular subsystem is the direct influence of temperature on the heart rate. The temperature of the pacemaker cells is known to influence heart rate. Since the thermoregulatory subsystem computes temperatures in the trunk core, this parameter is passed to the cardiovascular subsystem and is used to compute an additive term for the heart rate which is directly proportional to the change in the temperature. Selkurt (1963) indicates that the magnitude of this effect is approximately 7-11 beats per minute per 1°F .

The remaining parameters of the cardiovascular - thermoregulatory interface are passed from the cardiovascular subsystem to the thermoregulatory subsystem. The representation of the cardiovascular subsystem in the original thermoregulatory model was very crude and caused significant inaccuracies in its response. These inaccuracies were therefore expected to be relieved by interfacing the model with a fully developed cardiovascular model. This task presented some difficulty since the 28 compartments of the cardiovascular subsystem had relatively little resemblance to the 40 geometrical compartments of the thermoregulatory subsystem. Correspondence was found, however, between the two systems on a more gross level. The blood flows which could be used directly from the cardiovascular model were the venous return from the brain and a sum of venous return flows from the heart, kidney, and liver. These two parameters were utilized as the head core and trunk core blood flows, respectively. The total muscle blood flow was also passed from cardiovascular to thermoregulatory as well as cardiac output. The muscle blood flow was distributed using the original distribution fractions in the thermoregulatory model as reported by Stolwijk (1971) for rest and for bicycle ergometry exercise. The remainder of the cardiac output was distributed to the remaining core and fat blood flows. This procedure provides a workable interface between the two models. However, in future studies, refinement of these blood flows using experimental data to acquire better representation of temperature distributions for transient response to exercise is recommended. A final parameter which is passed from cardiovascular to thermoregulatory subsystem is the metabolic rate. This parameter replaces an input variable to the original thermoregulatory subsystem which remained constant throughout an experiment. This refinement was also required in the thermoregulatory model to improve the transient response to exercise. The arterio-venous oxygen difference which is

computed in the cardiovascular subsystem includes consideration of such factors as oxygen debt, oxygen deficit, and oxygen uptake in working muscle. These interface variables give a much more accurate representation of the metabolic expenditures which result in the production of heat.

In summary, the cardiovascular - thermoregulatory interface addresses the shortcomings of the cardiovascular model in the area of skin blood flow during exercise and the shortcomings of the thermoregulatory model in the area of blood flow rates and the factors affecting metabolic utilization of oxygen. The principal result of an increase of skin blood flow in the cardiovascular subsystem is an increase in cardiac output which affects all other flows in the cardiovascular system. A primary benefit of this subsystem interaction should be realized when conditions of various levels of skin flow during exercise can be studied. In this study, the competitive effect of skin and muscle blood flow can be studied at various ambient temperatures for several levels of prolonged exercise and for other conditions.

Computer Program Architecture

Extensive planning for a software structure for the whole-body algorithm was required before it could be implemented. The program objectives call for a model which could simulate both long term adaptive changes and short term simulations of acute experimental stresses. The approach taken as previously outlined was to run the long term model for the desired amount of adaptation time and to initiate the short term models with its results. The short term models are then executed in a parallel or simultaneous fashion and important effects of the short term stresses are passed back to the long term model upon completion of the short term experiment for further simulation of the adaptive process. This procedure provides the structure whereby whole space flights may be simulated using the whole-body algorithm.

The total amount of computer code required for the whole-body algorithm was 29.2 K decimal words. In order to operate within the limits of a 20K core size (in the time-sharing mode), the program had to be overlaid. The overlay process, which is commonly used in the programming of operating systems, stores parts of the program out on mass storage devices (discs) until a specified portion of the program, a segment, is required during the execution. At that time, the segment is brought into core and utilized until another segment of the program is required. Using this technique, programs such as this one may have a total size which is much larger than the available core size. Figure 3-10 outlines the contents of the segments by subroutine names and gives relative sizes of the segments used and Table 3-1 provides an index of subroutines and common blocks. As can be noted in the Figure, the programs communicate with each other and update the variables which are changed during execution through the common blocks shown. The secondary advantage of this approach is that whenever the whole-body algorithm completes a short term experiment, control is returned to another segment in Level 1. Then, if the short term models are again called, the programs are returned to core in their initialized state as updated by the long term simulation so that a new short term simulation can begin without memory of the past simulation. This process assures that all computed variables are reset to their initial value without the need for adding additional computer code to the program to accomplish this function. In order to obtain synchronous operation of the short term subsystem models, an executive program was added. The function of the executive program is to compare the value of time in the various subsystems and advance the appropriate subsystem in time accordingly. The maximum difference in integration step sizes in the short term subsystems occurs between the cardiovascular (.002 sec) and the thermoregulatory (3 sec.). One subsystem may, therefore, have several integration steps before another is advanced by one step.

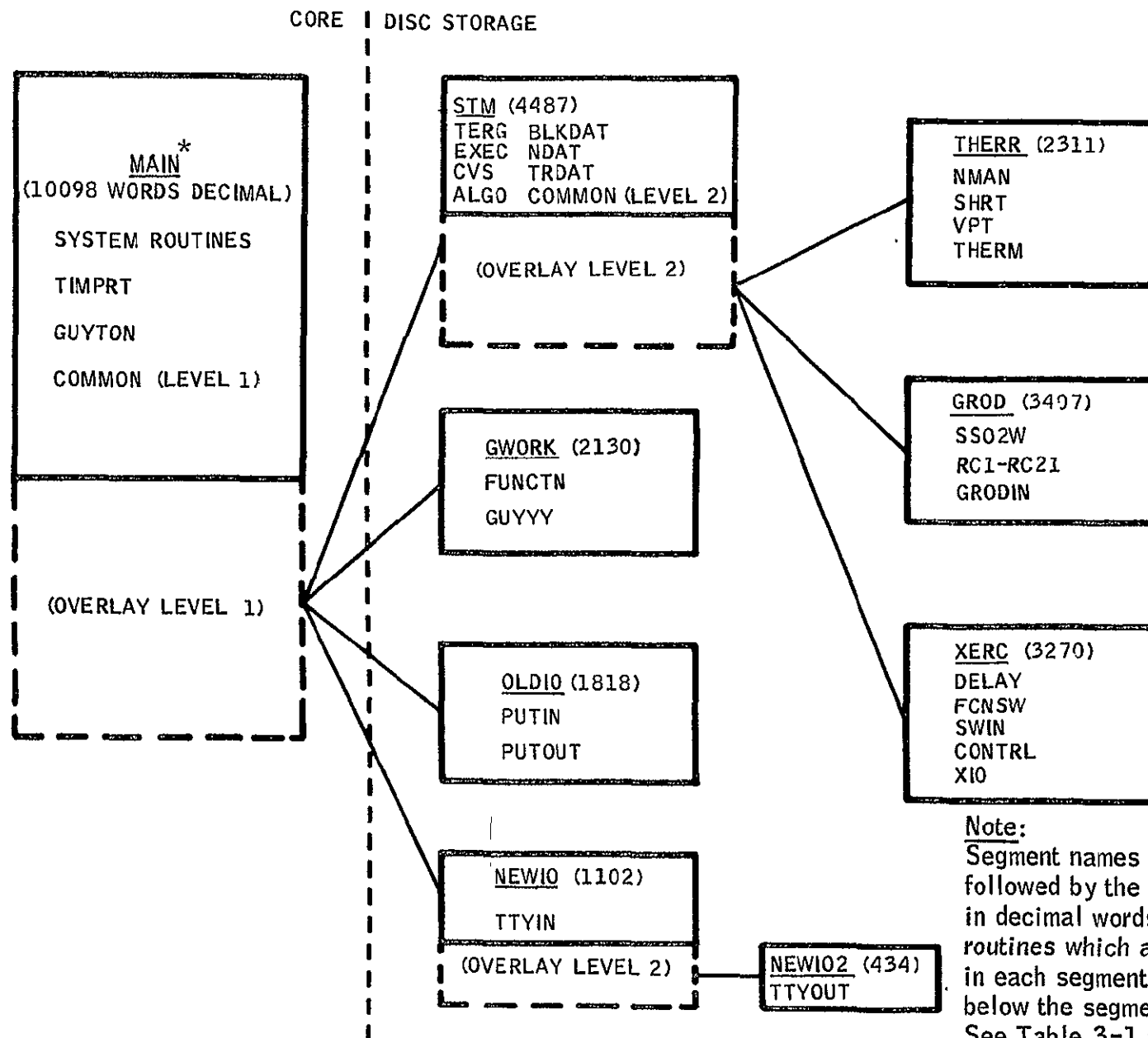


FIGURE 3-10 PROGRAM ARCHITECTURE

Note:
Segment names are underlined followed by the segment size in decimal words. The subroutines which are included in each segment are listed below the segment name. See Table 3-1 for an index of common and subroutine elements.

TABLE 3-1 COMMON BLOCKS AND SUBROUTINE
INDEX OF THE WHOLE-BODY ALGORITHM

<u>COMMON (Level 1)</u>	<u>COMMON (Level 2)</u>
STORE (Long Term)	TRM (Therm.)
DEMAND "	STATE (Cvs.)
NUMERO "	DELAYC (Cvs.)
ARRAY "	XIOD (I-O)
TAPE (Short Term IO)	Z (Resp.)
TOSHOR (Long Term-Short Term Interface)	R (Resp.)
TTYIOB (Long Term)	RINTR (Cvs-Resp. Interface)
PPPPPP "	TRINT (Cvs-Therm. Interface)
SEG11 "	

SUBSYSTEM INDEX OF SOURCE LANGUAGE PROGRAMS

<u>Long Term</u>	<u>Short Term</u>	<u>Cardiovascular</u>	<u>Respiratory</u>	<u>Thermoregulatory</u>
GUYTON	XIO (Input-Output)	TERG	NDAT	TRDAT
TIMPRT	EXEC (Executive)	CVS	GRODIN	THERM
FUNCTION		ALGO	SSO2W	SHRT
GUYYY		BLKDAT	SSVENT	NMAN
TTOUT		DELAY	RC1-RC21	VPT
TTYIN		FCNSW		
PUTIN		SWIN		
PUTOUT		CONTRL		

Input and Output Functions

When the four separate models were linked together, four different sets of input and output functions existed in the model. The disadvantages of this configuration were numerous and significant. Programming changes were required in several locations to consolidate and improve input and output functions. The input and output functions of the long term model, however, remained essentially unchanged with a few exceptions. A description of these changes and complete user instructions for the whole-body algorithm will be transmitted by separate TIR (TIR 741-MED-5009). The short term subsystems in contrast required extensive modification and consolidation of these functions in order to simplify operation for the user and to gain some efficiency in operation.

Duplication of certain inputs parameters was often required in the various short term subsystem models and these parameters were frequently required in different units. Among the variables which required multiple input were the experimental protocol values, model end time, and print intervals for each model. Furthermore, many different programming methods were being used to initialize the models. Also, a considerable delay in the model operation was caused by the computation of steady-state conditions in the thermoregulatory subsystem. These problems, and others, had to be resolved such that the flexibility to control required input and output functions was maintained in all the subsystems during all short term experiment simulations.

The solution to this problem was accomplished in several steps. First, all required input of experimental protocol parameters were consolidated into interactive sequences according to the chosen stress. In addition, a typical experimental protocol for each stress was stored in the program. The values of this stored protocol may be changed as desired by the user by responding appropriately to the queries of the

program. In this manner, input data are given in a consistent set of units and are used to define the experimental protocol in all the subsystems.

A second added feature is that parameters in the models, other than protocol, may be changed through an interactive set of input options. To change these various parameters in the models, the user must input the appropriate codes (index nos.) established for this purpose. These codes are given in the user's guide. Through this procedure such variables as postural changes, cabin environmental changes, inspired gas concentrations, and several hundred other model parameters can be changed to alter the conditions being simulated in each of the subsystem models or to simulate conditions of multiple stresses. One special case of this input feature allows the thermoregulatory subsystem to reach new steady-state conditions if environmental parameters are changed in the initialized data section.

The print interval for all of the subsystems is changed through another interactive question. The print interval controls the amount of simulation time elapsed before output is printed from the subsystems in a block format. This output block consists of one line of output from each of the three subsystem models. The contents of these lines are normally established by the program as a set of key parameters for each subsystem. However, other output variables may be selected when other output variables may be of interest to the user. This variable output option allows the user to choose from over 2000 different model parameters and variables in the short term experiment operation alone.

Once the short term experiment is concluded, control is returned to the long term subsystem for additional simulation, if desired. This sequence may be repeated as many times as the user desires. In this

manner, sequential long term and short term stresses may be used to simulate an entire space mission sequence or similar combination of adaptive changes and acute experimental stresses.

In addition to the printed output of the whole-body algorithm, optional output files may be created for graphics display of the output. This option gives the user the capability to save his output and use the more flexible general purpose graphics programs for display of the output in the format of his preference. These graphics programs are part of a Skylab data analysis system which is also maintained and operated by GE on the NASA/JSC Univac 1108 computer. The available graphics options of this system, described in TIR 741-MED-5003, offer a wide variety of graphic output formats for the user to choose from. This indirect method of graphic display for the whole-body algorithm offers some distinct advantages. Primarily, it allows the user to compare experimental data from the data base directly with model output from previous runs. The value of these powerful tools and the tremendous potentials potentials for hypothesis testing and model refinement is undoubtedly great, but cannot be fully appreciated until they are used.

4.0 VALIDATION OF THE WHOLE-BODY ALGORITHM

The validation process is primarily concerned with demonstrating the accuracy and capability of simulation models. An important aspect of validation involves comparing the behavior of the model's dependent variables with their experimental counterpart for the same stress. Differences between model behavior and experimental data can often be corrected or minimized by either introducing new elements into the model's structure that were previously omitted or by modifying the existing structure (i. e. , adjusting the value of parameters that are not well known). Both of these types of changes were necessary in validating the present model and in all cases the changes were consistent with known physiological processes.

The extent to which the validation process can be carried is limited by the data in the available literature. Thus, if only steady-state data are available, validation in the dynamic or transient mode cannot be performed, even though the model has that capability. Similarly, if only a relatively small number of experimental variables have been measured during a particular stress, then it is possible to validate the model for the responses of only those measured variables; the model's simulation of all other variables can be obtained, but should be considered as predictions which await experimental verification. The response of the body to a given stress is almost always related to the level or intensity of that stress, and more often than not, this relationship is nonlinear. Therefore, in order to validate the model properly, it is desirable to obtain data not merely for a given stress, but for a range of intensities of that stress. If it is important to simulate more than one stress, as in this study, the validation process will result in a more accurate model if the experimental response of the same variables are known for each of the desired stresses. Thus, an idealized set of experimental

data suitable for complete validation of a model as complex as the one considered here should include:

- a) steady-state data
- b) transient data
- c) data for a wide range of stress intensities
- d) data for all of the major dependent variables of interest or importance
- e) data for a variety of stresses

In addition, since experimental protocol, measurement techniques, and number and type of subjects may vary widely from one investigation to another even when studying the same stress, it is desirable to obtain much of this data from the same experimental study.

It was apparent from the outset that it would be impossible to obtain the idealized data set required for completely evaluating and validating the whole-body algorithm. The literature search, which consumed a considerable portion of time, resulted in the discovery that:

- a) very little transient data were available for any of the stresses,
- b) responses to graded levels of stresses were not available for many of the cases considered except for a few easily measured variables such as heart rate and ventilation rates,
- c) experimental studies were almost always concerned with only one major physiological system and entirely neglected other important systems; thus, a paper which reported cardiovascular responses to graded levels of environmental temperatures failed to report body temperatures or ventilation rates.

In many cases, it was impossible to obtain confirmatory data and validation was based on a single source. The task of validating the whole-body algorithm turned out to be more difficult than validation of many other physiological models merely because it is more complex than most other models, containing more subsystems, more parameters, and more dependent variables.

All the short term stresses chosen for simulation were similar to those that have already been used to validate at least one of the short term subsystem models when they were operated by themselves. A summary of the short term models and the corresponding stresses for which they have been tested on a stand-alone basis is shown in Figure 4-1. If validation were restricted to merely testing those subsystems of the whole-body algorithm which have previously been tested, the data collection and validation task would have been simpler since a portion of the necessary data were available and documented. However, all of the models were not previously capable of responding to all of the stresses as indicated by the boxes labeled "WBA" in Figure 4-1. The formulation of the whole-body algorithm has increased the capability of each of these models and provided a basis, through the interfacing links and simultaneous operation of all the models, for simulating additional stresses in an integrative manner. For example, the thermoregulatory model has been previously validated for a thermal stress at rest; however, the respiratory and cardiovascular subsystem model previously had no capability to simulate thermal stresses. Thus, the data collection and validation process needed to be extended to include responses of these additional subsystems. Unfortunately, as previously discussed, physiological studies of whole-body integrated responses to stresses is lagging far behind its potential and much of the desired data were unavailable. Nevertheless, a wide variety of responses have been tested and the overall capability and potential of the whole-body algorithm is evident from the results presented in this section.

In a model as versatile and complex as the whole-body algorithm, it is possible to test an endless variety and combination of situations, stresses, parameter changes, etc. In order to limit these tests to a reasonable number, adhere to the requirements and objectives stated in Section 2.0 and still demonstrate the validity of the model, the

CAPABILITY OF SHORT TERM SUBSYSTEM MODELS
TO SIMULATE SHORT TERM STRESSES BEFORE AND AFTER
INCORPORATION INTO WHOLE-BODY ALGORITHM

MODEL	STRESS					
	LBNP	TILT	HYPOXIA	HYPERCAPNIA	THERMAL STRESS	EXERCISE
Cardiovascular Subsystem	X	X	WBA	WBA	WBA	X
Respiratory Subsystem	WBA	WBA	X	X	WBA	X
Thermoregulatory Subsystem	WBA	WBA	WBA	WBA	X	X

X = Stresses for which subsystem has been previously validated on stand-alone basis.

WBA = Additional capability due to integration of subsystems into whole-body algorithm

FIGURE 4-1

following restrictions were imposed: a) only one stress at a time would be imposed on the model; multiple stress simulations, such as exercise in a hot environment, would not be performed, b) a number of relevant short term stresses will be used to validate all three of the subsystem models in the short term section of the model while the long term portion of the model would be validated with only a single stress, c) the emphasis on validation would be in the steady-state domain although the capability to simulate dynamic changes will be demonstrated, d) while the model will have the capability to perform experiments of short duration with the short term subsystems and pass changes representing a new physiological steady-state to the long term subsystem, this capability will not be validated; thus, no attempt was made to determine long term fluid-electrolyte changes or other adaptation effects as a result of thermal stress, hypoxia, etc., e) the reverse situation, automatically reinitializing the short term subsystem models with changes resulting from a long term stress, would be validated with a pre- and post-bed rest exercise and tilt stress following several simulated weeks of bed rest. This simulation will demonstrate the capability of the long term subsystem for dynamic adaptation of certain elements such as pressure receptor resetting, autoregulation of blood flows, and stress relaxation.

Figure 4-2 summarizes information related to the validation tests performed under these guidelines.

4.1 SIMULATION OF LBNP AND TILT

Physiological Response to Tilt and LBNP

The physiological changes that occur when an individual assumes the erect position provide a hemodynamic stress on the entire circulatory system. The ability of the vasculature, heart, and nervous system to appropriately react to this stress forms the basis of the tilt-table test and the lower body negative pressure (LBNP) test.

WHOLE-BODY ALGORITHM VALIDATION TESTS

	LBNP	TILT	HYPOXIA	HYPERCAPNIA	THERMAL STRESS	EXERCISE	BED REST	COMBINATION BED REST + PRE- AND POST-EXERCISE & TILT
SIMULATION FORCING FUNCTION	↓ Extra-vascular pressure	↑ Gravity Vector	↓ pO_2 Inspired Air	↑ pCO_2 Inspired Air	↑ Ambient Temperature	↑ External Work Load	↑ Vascular Stressed Volume	Combined bed rest, tilt and exercise + automatic sequencing between long & short term subsystems
PRIMARY WBA SUBSYSTEMS VALIDATED	Short Term (Cardiovascular)	Short Term (Cardiovascular)	Short Term (Respiratory, Cardiovascular)	Short Term (Respiratory, Cardiovascular)	Short Term (Thermoregulatory, Cardiovascular, Respiratory)	Short Term (Thermoregulatory, Cardiovascular, Respiratory)	Long Term	Long Term + All short term subsystems
DURATION OF SIMULATION	5 min.	5 min.	7 min.	7 min.	6 hours	30 min.	28 days	28 days
STRESS INTENSITY VALIDATED	-30 mm Hg to -50 mm Hg	70° Tilt	8% O_2	7% CO_2	20° C to 43° C	0 Watt to 200 Watt	Δ Stressed Volume =300 ml	Δ Stressed Vol. = 300 ml + 70° tilt + 50 watt exercise
DYNAMIC MODE TESTED T = transient S = steady-state	S	S	S	S	S	S,T	S,T	S

FIGURE 4-2

Upon shifting from supine to erect position changes occur in circulatory pressures and flows as well as in blood volume distribution. The arterial, capillary, and venous pressures become markedly elevated in the dependent extremities causing a net capillary filtration into the tissues. This can result in a loss of 5 - 10% of the supine blood volume (Piemme, 1968). An additional 10% of blood volume is shifted from the upper part of the body (mainly from the thoracic cavity) to the legs, where it is pooled primarily in the distensible venous segments (Sjostrand, 1953). Venous segments below the heart tend to distend while those above the heart tend to collapse. Unless compensatory mechanisms come into play, the effective central venous pressure would probably fall below that of the heart, resulting in insufficient cardiac pumping and orthostatic hypotension.

The defenses of the body against orthostatic hypotension consist of both passive and active elements (Guyton, 1973; Rushmer, 1961; Piemme, 1968). Ultrafiltration into the tissues is minimized by: a) increasing tissue fluid pressure, b) increasing lymphatic flow, c) reduction of the hydrostatic columns in veins by "pumping" blood past leg venous valves and d) transient venoconstriction of the extremity venules. Systemic arterial pressure is maintained, and even elevated, due to activation of intrathoracic and carotid blood pressure receptors. The reduction in effective blood volume caused by a shift of blood from the upper to the lower part of the body is associated with a sustained increase in sympathetic activity to the resistance vessels in muscles and visceral organs and to the heart, thus maintaining cardiac output and arterial blood pressure in spite of reduced cardiac filling pressure. The increase in leg vascular resistance also helps minimize venous pooling. Central venous pressure must be maintained to promote adequate right ventricular filling. The exact mechanisms controlling this important adjustment have not yet been elucidated, but it is believed that the following factors

are important in preventing a debilitating fall in central venous blood volume and pressure: a) contraction of large venous channels and venous reservoirs such as exist in the visceral organs; b) external compression of veins by skeletal muscles in the legs, and c) an external pressure on the large abdominal veins exerted by the increased hydrostatic column of abdominal organs as well as an increase in abdominal muscular contraction. The net result of the effects induced by standing or tilting and the influence of the orthostatic defense mechanisms is a reduction in central blood volume, a decreased cardiac output due to reduced stroke volume and in spite of an increase in heart rate, and an increase in peripheral resistance which acts to elevate the mean systemic blood pressure (Lamb, 1968). Orthostatic hypotension develops when one or more of the compensatory mechanisms is not adequate - this subject is the concern of present physiological studies.

Lower body negative pressure tests, in which a decreased transmural pressure is created in the blood vessels below the waist, can also cause a considerable degree of venous pooling in the lower extremities, similar to that found in tilt-table experiments (Wolthuis, et al, 1975). Many other hemodynamic changes are similar, such as decreases in cardiac output and stroke volume and increases in heart rate. However, many investigators believe that there are certain fundamental differences between these two stresses (Wolthuis, et al, 1974; Blockley, 1970). The most important difference is that a hydrostatic gradient exists in tilt, but does not in LBNP. The tilt experiment causes a gravity gradient from the heart to the extremities in every vascular segment with varying amounts of blood pooling depending on the length of the segment and its distance from the heart. The effect these two different kinds of stresses have on the cardiovascular system will be evident in the results presented below. LBNP has been used in experimental studies as a means of creating an effective hemorrhage in the central portions of the vasculature (Murray, et al, 1968), as well as providing a hemodynamic stress for crewmen in weightless space flight.

Simulation of LBNP/Tilt with the Whole-Body Algorithm

The tilt experiment is simulated in the short term subsystem model by applying the gravity pressure head terms to the vascular compartments. The overall effect is a decrease in blood volume above the heart and an increase in all segments below this region. The simulation of LBNP is accomplished by applying a negative pressure term external to the leg vessels which increases the transmural pressure and results in a calculated volume increase in blood volume of the leg compartments.

The cardiovascular subsystem model contains representations of many of the elements previously discussed that are involved in the physiological response to tilt and LBNP. Thus, there are elements that simulate: a) the shift in blood from upper to lower segments of the body, b) the baroreceptor reflex and the resulting sympathetic effects on heart and vasculature, c) the muscle leg pump, d) venous valves, e) collapsible and distensible veins, and f) stress relaxation. There is no representation of extravascular compartments in the short term models and hence, no simulation of transcapillary filtration and lymph flow. The disadvantages imposed by this limitation are more apparent than real for several reasons: a) filtration into the tissues upon standing is not a rapid process, taking up to 30 minutes before the process reaches a steady-state (Lamb, 1968), b) the baroreceptor reflexes are fully developed within the first minute following postural changes (Guyton, 1973), and c) most measurements of hemodynamic variables during LBNP and tilt are usually completed within the first five minutes following the stress well before the major effect of ultrafiltration is felt. Furthermore, while tilting may result in extravasation of plasma there is no conclusive evidence that the same is true during LBNP. Thus, the only real limitation that exists in simulating tilt is that the model's response should be compared to experimental measurements taken within several minutes after the stress is imposed.

Comparison of Whole-Body Algorithm Simulation of Tilt and LBNP
with Available Data

The primary responses to LBNP and tilt occur in the cardiovascular system. No noteworthy changes are seen in ventilation rates or thermal regulation. Changes in several important variables of the cardiovascular system are shown in Figures 4-3 and 4-4 where the model's response is compared to experimental data from a variety of sources. It is obvious that agreement between the various experimental studies is far from perfect. Nevertheless, there are some dramatic changes that occur during these stresses and different responses can be seen between the tilt and LBNP experiments. Most of these changes and differences are reproduced by the simulation response. Both LBNP and tilt cause increases in heart rate and decreases in stroke volume. The changes in heart rate for the higher levels of LBNP are similar to those observed for 70° tilt, but the stroke volume decreases are more severe during tilt. A more dramatic difference between these two stresses, however, is seen in the blood pressure responses. The tilt case results in a large increase in diastolic pressure and little change in systolic pressure while during LBNP there is a substantial drop in systolic compared to the changes in diastolic pressure. As mentioned previously, the main difference between the simulation of these two stresses lies in the different hydrostatic gradients that are imposed on the blood columns. In particular, the pressure receptors located headward above the heart are extremely sensitive to changes in hydrostatic pressure. During the onset of LBNP, blood pressure changes are induced primarily because of depletion of central blood volume, while during tilt, pressure changes occur due to both fluid volume and gravity vector changes. The sympathetic response of the model is, therefore, quite different to these two stresses and compares favorably with the data from most investigations.

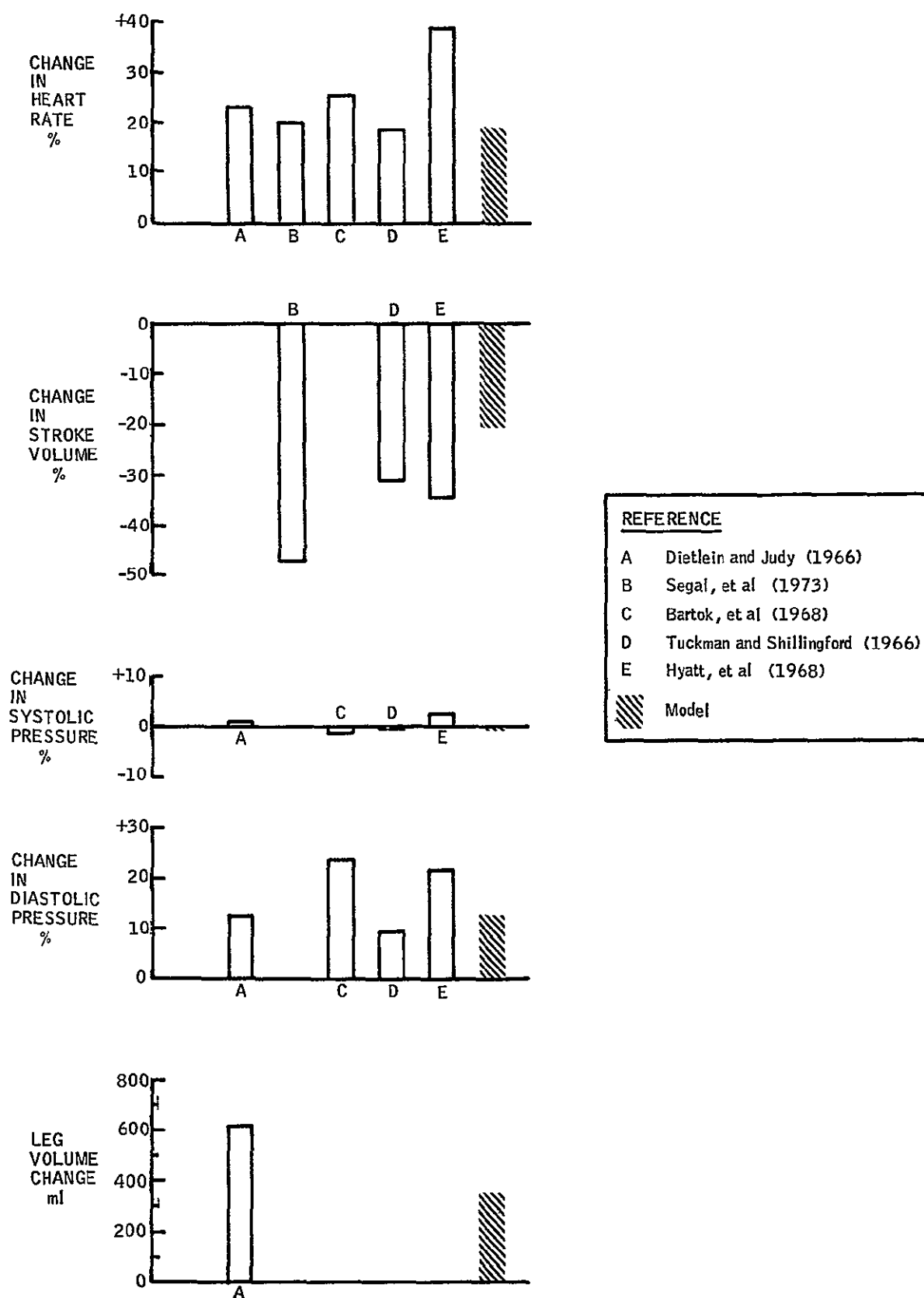


FIGURE 4-3 EFFECT OF 70° TILT ON CARDIOVASCULAR RESPONSE: MODEL VS. DATA

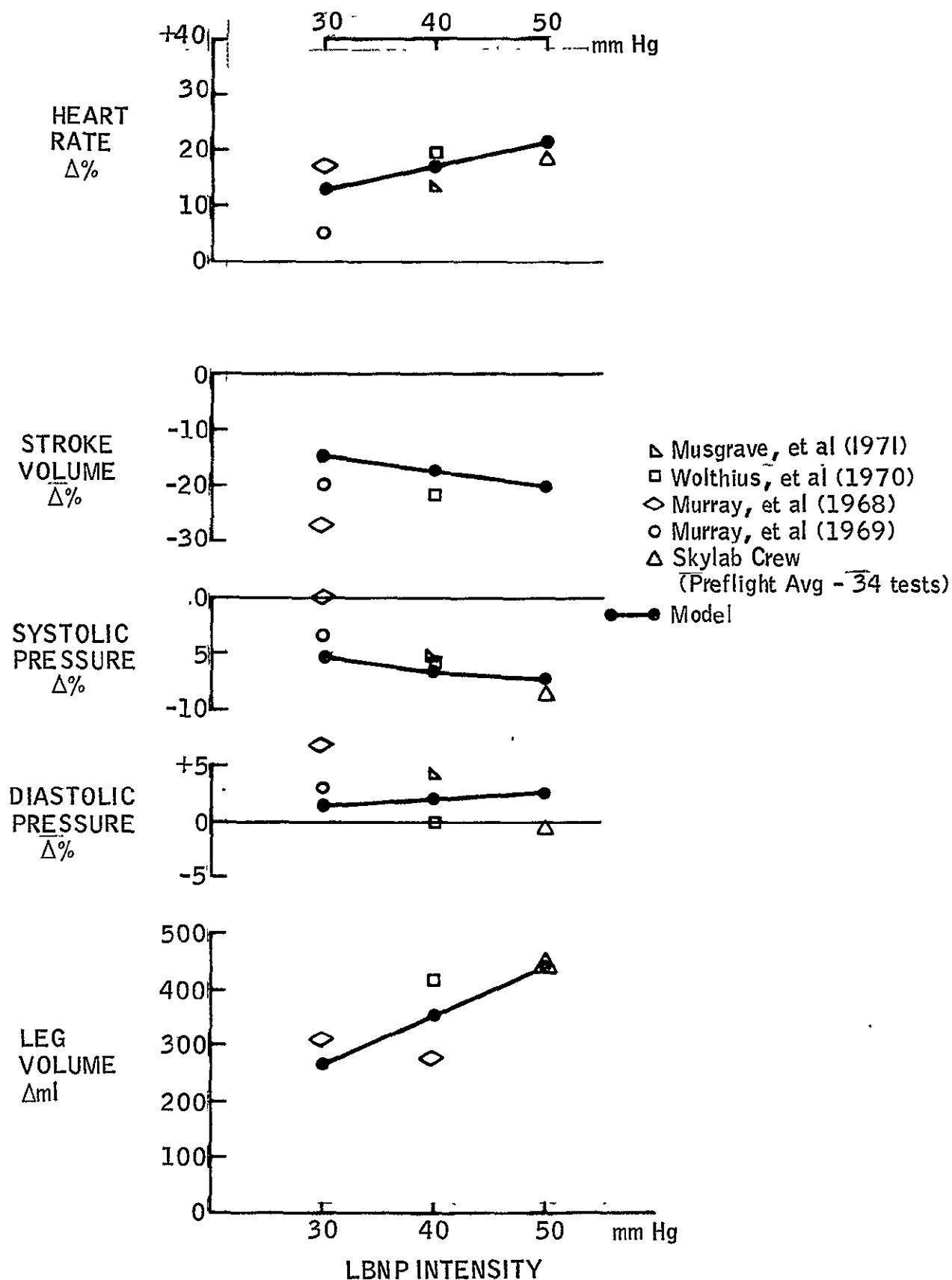


FIGURE 9 EFFECT OF LBNP ON CARDIOVASCULAR RESPONSE: MODEL VS. DATA

4.2 SIMULATION OF RESPIRATORY GAS DISTURBANCES-HYPOXIA AND HYPERCAPNIA

Physiological Response to Hypoxia

An adequate supply of oxygen is essential to meet the varied metabolic requirements of every body cell. Oxygen transport from the inspired air to the individual cells involves many processes and organs, each with their own regulatory system. The essential components of the oxygen supply system are: a) ventilatory gas exchange, b) the cardiovascular system including cardiac pumping capability and blood flow distribution, c) hemoglobin affinity for oxygen, and d) hemoglobin concentration. All of these elements are present in the whole-body algorithm in varying degrees of detail. In the normal subject this complex system is adjusted to maintain an adequate tissue oxygen tension that meets the tissue requirements for the body as a whole. In the stressed individual in which either metabolic requirements or oxygen supply are abnormal (as in exercise, hypoxia, anemia, etc.) the system readjusts its oxygen supply capability to maintain adequate oxygen supply to the more critical organs such as the heart, brain, and in the case of exercise, the muscle tissue (Finch & Lenfant, 1972).

The most common experimental method to induce hypoxia (an inadequate oxygen supply to the tissues) is by decreasing the oxygen content of the inspired gas. Since oxygen transport to the body cells is ultimately governed by diffusion which is dependent upon the partial pressure gradient, the critical indicator of oxygen level is its partial pressure (both in the inspired air and in the blood) rather than the absolute concentration ($\text{ml O}_2/\text{ml blood}$). Breathing air with less than normal oxygen will not cause noticeable effects either in pulmonary ventilation or in overall cardiovascular function until the inspired pO_2 level falls from its normal value of 158 mm Hg to below 100 mm Hg (corresponding to an inspired oxygen concentration of 14 percent and

an arterial blood pO_2 of about 60 mm Hg.) Thus, mild acute hypoxia is not considered a strong stimulus for physiological response (Dripps and Conroe, 1947). Inhalation of 7 - 10% oxygen results in moderately severe hypoxia with an arterial pO_2 of 30 - 40 mm Hg. Some of the more noticeable acute physiological effects are a sharp increase in pulmonary ventilation and a large rise in heart rate as well as cardiac output (Abramson, 1967). The small changes in blood pressure that accompany this stress (both slight increases and decreases have been observed) suggest that considerable vasodilation has occurred (Kontos, 1967). Little quantitative information is available for man regarding the redistribution of blood that results in overall peripheral vasodilation. In general, blood is believed to be shunted to tissues with high oxygen extraction (heart, muscle, and brain) at the expense of flow to tissue with low oxygen extraction (skin, splanchnic, and kidney). Severe hypoxia, occurring at arterial oxygen partial pressures of 20 - 25 mm Hg, results in a reflex bradycardia and large vasoconstrictor effect. This summary and model validation will not be concerned with these extreme effects.

The body has developed a complex of regulating systems which are integrated both at the central nervous system level and the local organ level. It is generally accepted that the hypoxia induced increase in ventilation is a direct result of a decreased arterial pO_2 causing increased peripheral and central chemoreceptor activity (Duffin, 1971). There is much less known about the determinants of the accompanying cardiovascular changes. For many years, it was believed that the chemoreceptors were mainly responsible for bringing about most of the cardiovascular effects of hypoxia (or hypercapnia), but such a view is no longer tenable. Figure 4-5 summarizes the effects of these and other factors on the heart, the resistance vessels and the capacitance vessels (compiled from the following sources: Abramson, 1967; Shepherd, 1963; Sagawa, 1969; Hatcher and Jennings, 1966; Korner, 1971, and Scher, 1974).

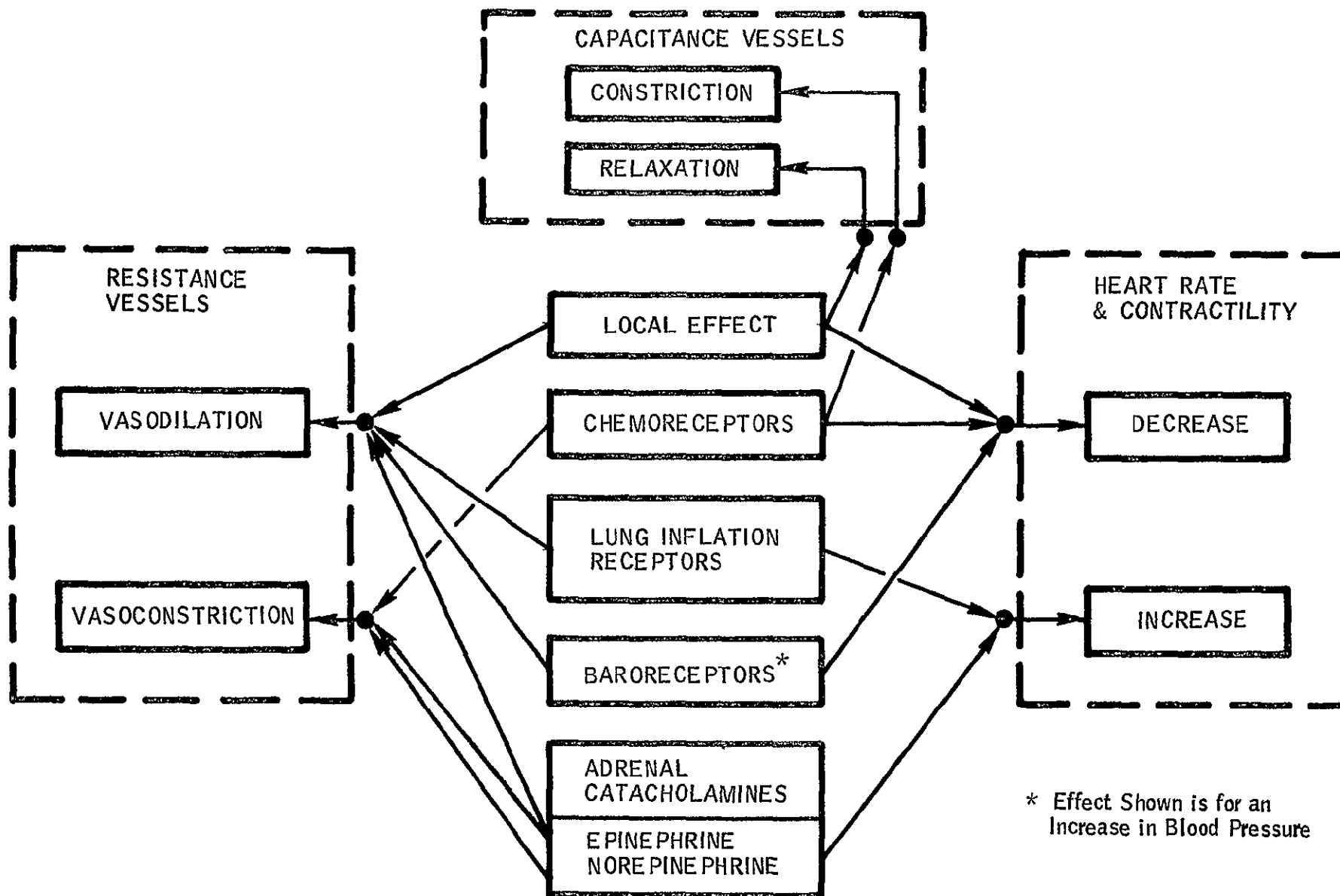


FIGURE 4-5 DETERMINANTS OF CARDIOVASCULAR REGULATION DURING HYPOXIA AND HYPERCAPNIA

Figure 4-6 provides a schematic view of the integration of these factors during the hypoxic stress. It is obvious that the chemoreceptors provide only a part of the control necessary to withstand a decrease in oxygen supply. The actual degree and direction of cardiac and vasomotor behavior depends on the degree of hypoxia, the particular vascular bed, the animal species under investigation as well as the relative influence of these competing local, autonomic, and hormonal factors. It is experimentally difficult to separate the various autonomic effects and little quantitative information is available regarding the relative influence of these determinants in man.

A complicating factor which must be considered is the fact that under the influence of low blood pO_2 the respiratory minute volume output increases and consequently carbon dioxide is blown off in greater than normal amounts. Thus, hypoxia is usually associated with hypocapnia which is known to cause variation in central nervous activity, often in a direction that minimizes some of the cardio-respiratory effects of hypoxia (Sagawa, 1969; Reynolds and Milhorn, 1973).

Physiological Response to CO_2 Inhalation (Hypercapnia)

Carbon dioxide is a substance that is normally inspired in extremely small quantities (0.5% or 4 mm Hg partial pressure). However, because large quantities are produced in the body by cell metabolism the partial pressures in the blood are relatively high, approximately 40 mm Hg and 46 mm Hg in arterial and venous blood, respectively. It is generally believed that blood CO_2 is one of several important chemicals used by the body to indicate local and overall rates of metabolism. CO_2 appears to be one of several sensing agents in various feedback pathways that adjust vascular resistance and blood flow to supply sufficient oxygen to meet the demand and carry away toxic products of metabolism. During

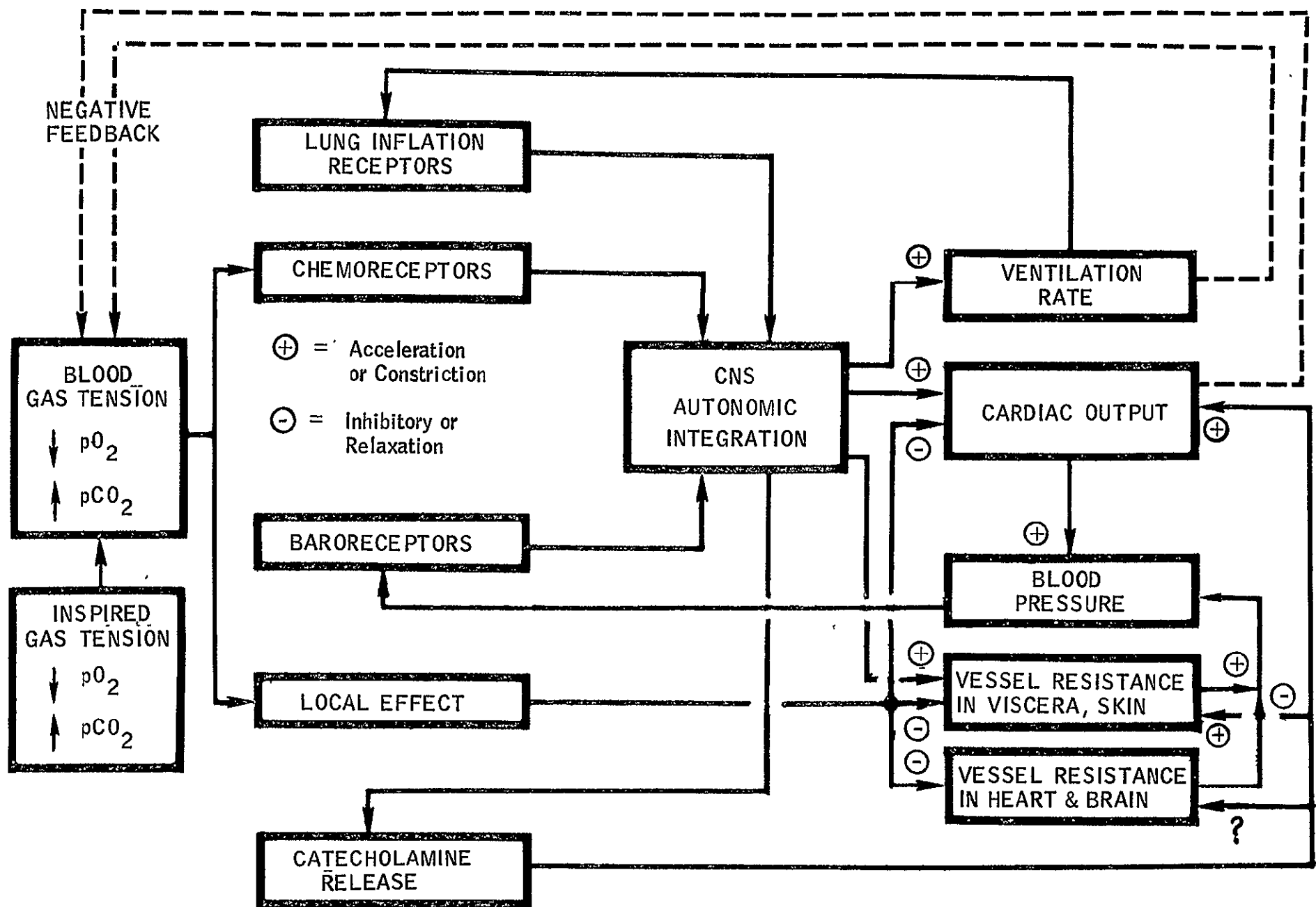


FIGURE 4-6 INTEGRATED CARDIO-RESPIRATORY REGULATION DURING HYPOXIA OR HYPERCAPNIA

acute hypercapnic stress the resting individual is confronted with an unfavorable environment for the elimination of metabolic CO_2 and must increase minute ventilation. The body responds to acute CO_2 inhalation in many ways as if metabolism has suddenly increased such as in exercise or as if an accumulation of metabolites has occurred by local occlusion of blood vessels. Besides the ventilatory response, other observed changes include increases in blood pressure, heart rate, stroke volume, and cardiac output with a decrease in overall vascular resistance (Richardson, et al, 1961). Except for the marked increase in blood pressure, the overall response is similar to those previously described for hypoxia. Unlike oxygen, which does not appear to cause significant whole-body responses until its blood partial pressure has been reduced to about 40% of normal levels, the response to CO_2 is more linear and dramatic changes can be observed when blood pCO_2 changes only slightly from normal physiological values (Duffin, 1971).

While the ventilatory response to both hypoxia and hypercapnia have been well studied and essentially understood (primarily a chemoreceptor activated response) there have been far fewer studies of the cardiovascular effects of these disturbances, particularly for CO_2 inhalation. Except for the brain (which is under local rather than autonomic control) little attention has been paid to blood flow redistribution during hypercapnia. It appears that the same mechanisms activated by breathing oxygen poor mixtures are also activated by increases in carbon dioxide levels and act in very much the same way, but here too, little quantitative information is available in man (Sagawa, 1969). The scant attention paid to the cardiovascular system during hypercapnia has presented a severe challenge to the modeling task. For example, while peripheral blood flow resistance is known to decrease during hypercapnia, it is not clear how this occurs since the few available studies in man have suggested that only the brain and heart are known to vasodilate (Richardson, et al, 1961).

Simulation of Hypoxia and Hypercapnia with the Whole-Body Algorithm

The respiratory model was capable of simulating reasonable ventilatory responses to hypoxia and hypercapnia prior to its incorporation into the whole-body algorithm. The controlling mechanism was a chemoreceptor sensor responding to low levels of oxygen and high levels of carbon dioxide. However, the cardiovascular subsystem was not capable of responding to changes in blood gas tensions and additional modeling was required to account for this effect. In attempting to cope with the lack of qualitative data regarding mechanisms controlling the cardiovascular system and with few previous modeling guidelines to follow, it was decided that only a gross approximation of the real system was justified. The first major assumption was that the feedback systems (see Figures 4-5 and 4-6) responding to low levels of oxygen, whether they be local, humoral, or autonomic elements, also responded to increasing levels of carbon dioxide in the same qualitative manner. For example, it was assumed that both hypoxia and hypercapnia produce a local vasodilating effect and a depressant effect on the heart. While all the evidence is not yet available to support this assumption in its entirety, there is little contradictory evidence. The second major assumption was that, for the purposes of this preliminary study, it would be possible to lump many of these effects together into an effective "chemoreceptor" feedback pathway. The sensor of this pathway would have a graded response to increasing arterial levels of carbon dioxide and decreasing levels of oxygen, similar to the chemoreceptors of the ventilatory system, although the sensitivities to each of these gases as well as the manner in which they effected the target organ would depend on available data regarding integrated effects in the intact animal. The actual level of oxygen and carbon dioxide tension that exists in the blood at any moment would be obtained from the respiratory model which had previously been

shown to provide good agreement with published studies. In terms of the elements shown in Figure 4-5, the cardiovascular "chemoreceptor" was used to present a combination of local effects, chemoreceptor effects, the lung inflation reflex, and the effects of the adrenal catacholamines. The baroreceptor representation in the model was not changed and could function independently of the "chemoreceptor". Figure 3-7 summarizes this configuration in the whole-body algorithm.

In order to appropriately simulate the data available for hypoxia and hypercapnia in normal resting man, it was necessary to allow the chemoreceptors to effect heart rate, cardiac contractility, muscle flow resistance, renal flow resistance, and the resistance of flow through bone and fat in a manner generally seen in experimental animals. Since the sensitivities of the "chemoreceptors" to oxygen and carbon dioxide were not the same it should not be expected that these feedback pathways would respond in an identical manner for both hypoxia and hypercapnia.

Brain blood flow was a variable already controlled by the respiratory subsystem and no changes were necessary in that section of the model. A "chemoreceptor" effect on coronary and skin blood flow was not included in spite of data that demonstrated changes in these organs. Since their basal flow was so small compared to cardiac output it was felt that their effect on the overall system would be minimal. Further details of the modeling formulation have been presented in Section 3.0.

Simulation of hypocapnia and hypoxia was accomplished simply by changing the values of the parameters representing inspired air concentrations of O_2 , CO_2 , and N_2 .

Comparison of Whole-Body Algorithm Simulation of Hypoxia and Hypercapnia with Available Data

A review of the literature revealed no single study in which combined respiratory-cardiovascular effects were measured in response to graded

levels of either hypoxia or hypercapnia in normal man. The best available data for hypoxic responses are that of Reynolds and Milhorn (1973) for ventilatory response and Kontos, et al (1967) for circulatory responses. Data regarding the ventilatory hypercapnia response may be found in Reynolds, et al (1972) while Richardson, et al (1961) describes the cardiovascular response to CO_2 inhalation. Although the papers by Reynolds show the transient ventilatory response to graded changes in oxygen and carbon dioxide levels, the papers describing circulatory changes merely tabulated the overall responses for a single level of gas tension corresponding to breathing 8% oxygen in nitrogen and 7% CO_2 in air, experimental measurements being made only once at 7 minutes following the start of inhalation of the special mixture. Thus, limited by the available data, model validation was attempted for these two cases: hypoxia simulated with 8% oxygen in nitrogen and hypercapnia simulated with 7% CO_2 in air. The simulation and experimental results were compared at the seven minute level and are shown in Figure 4-7. Agreement between model result and data is very good for all cardio-respiratory variables and for both stresses. The major differences between hypoxia and hypercapnia appear to be a much lower blood pressure change for the former and a much higher ventilatory response for the latter. Brain blood flow is also considerably increased during the hypercapnia stress. The large increases in cardiac output shown are not all due to direct effects on the heart. Analysis of the simulation experiments has shown that decreasing peripheral resistance alone will account for a significant portion of the changes in cardiac output.

It is unfortunate that, due to data limitations, validation was possible for only a single inspired gas composition and for a single point in time for each of these stresses. This is a serious limitation to the modeling process and it certainly does not represent a complete challenge to a model capable of simulating dynamic responses to a wide range of

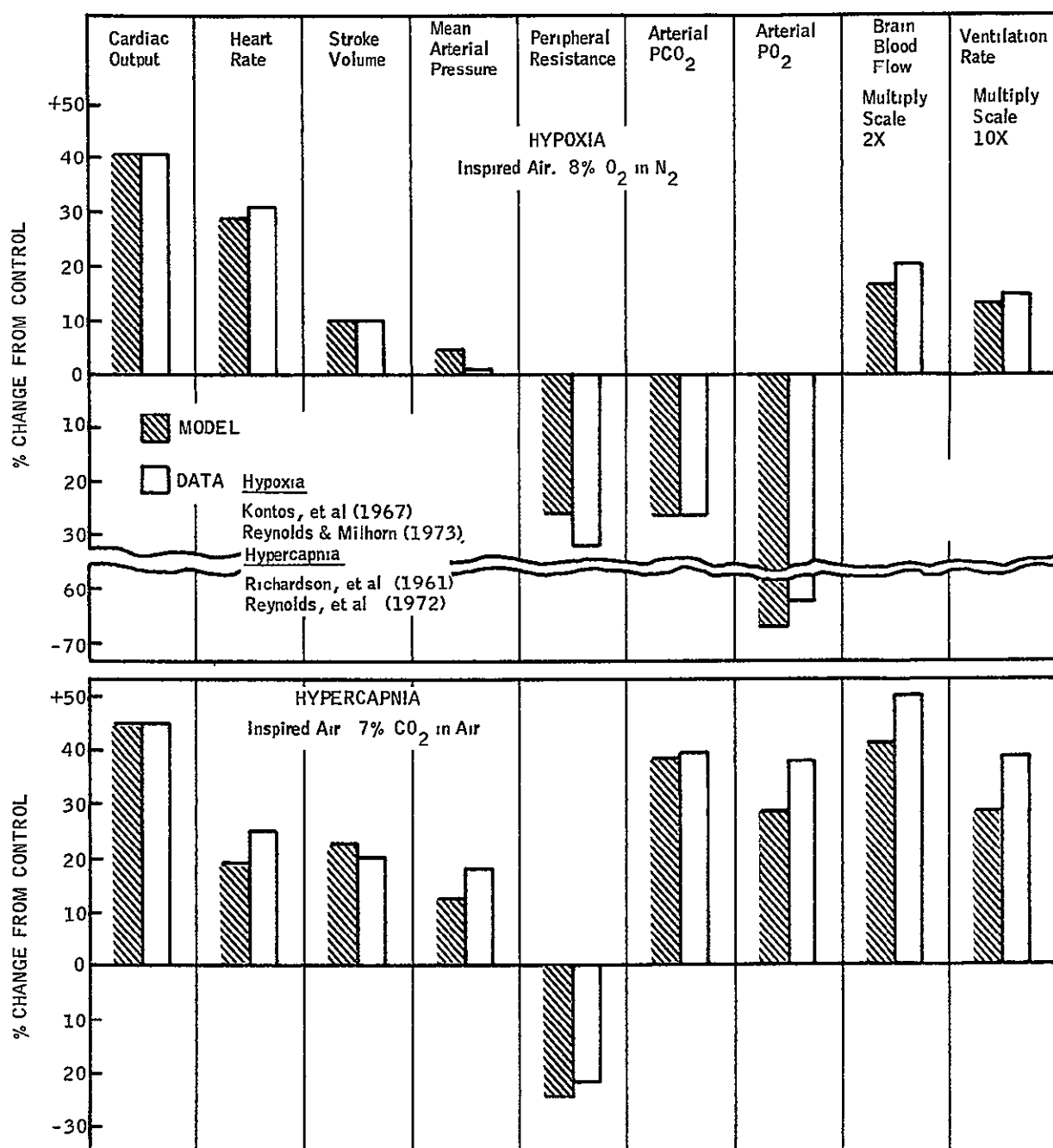


FIGURE 4-7 EFFECT OF HYPOXIA AND HYPERCAPNIA ON CARDIORESPIRATORY RESPONSE: MODEL VS. DATA

stress intensities. Nevertheless, it is important to keep in mind that the results achieved here are significant inasmuch as the same structural changes that were made in the model to simulate the hypoxic stress were used to perform an accurate simulation of the hypercapnic stress.

At the outset it was not expected that the physiological mechanisms underlying the cardiovascular response to hypoxia or hypercapnia would be so complex or that so little of the quantitative information needed for proper modeling of these mechanisms would be available. However, it became apparent that even if these mechanisms were known the task of predicting an integrative dynamic response pattern to varying degrees of hypoxia and hypercapnia would be beyond intuition due to the many competing elements involved. It is in just such a situation that modeling and simulation would contribute very real advantages. Preparing for this eventuality was one reason that a relatively detailed account of the qualitative aspects of these stresses was presented at the beginning of this section in spite of the gross simplifications that were eventually required.

4.3 SIMULATION OF THERMAL STRESS

Physiological Responses to Thermal Stress in Resting Man

If a thermal stress is imposed upon resting man by exposing him to a hot environment for short periods of time, changes are observed not only in the thermal regulating system, but in other major physiological systems as well, notably the circulatory and ventilatory systems. Indeed, in a strict sense, all of these subsystems act as a functional unit in order to reduce the thermal stress on the body. Thus, sweating, insensible heat loss from the lungs, redistribution of blood flows notably to the skin tissues, and a cardioacceleration, are all manifestations of thermoregulation and require a multiple system of regulating loops (Benzinger, 1969; Thauer, 1962).

The effects of heat exposure are first manifested by an increase in skin temperature. As further heating takes place the temperatures in all deeper tissue masses also tend to increase. In response, the body initiates certain adjustments (see Figure 4-8) that act to remove this excess heat load and reduce its effects: 1) blood flow through skin tissue increases as a result of both local and centrally mediated effects. This brings greater quantities of warm blood to the body surface where its thermal energy can be transferred through the skin and ultimately, by radiation and conduction to the environment. The normal skin flow of 150-200 ml/min can increase to 3500 ml/min and perhaps higher under maximum vasodilation (Rowell, 1974); 2) the increase in skin blood flow tends to increase skin temperatures. If the environment is warmer than the body surface (i. e., greater than $32-34^{\circ}\text{C}$), the body will gain heat by conduction and radiation; if cooler, it loses heat. Radiation is usually the more important route of heat exchange. 3) at ambient temperatures above $32^{\circ} - 34^{\circ}\text{C}$ circulatory adjustments alone are not adequate for dissipating heat by radiation because of the reduced or negative temperature gradient between skin and surroundings. At these temperatures sweating is initiated and its evaporation removes heat from the body surface. Evaporative heat loss by sweating is a particularly effective cooling mechanism. Maximum sweating levels for nude resting man approaches 400 ml/hr at ambient temperatures of 48°C representing about 270 watts of cooling power (Selkurt, 1971). At these high temperatures sweating and pulmonary water loss become the only avenues of heat loss. A humid environment and clothing both decrease evaporation of sweat and increase the heat load, while an increase in free air velocity on the skin does the reverse. The major circulatory change appears to be a shift of blood flow from the central to peripheral vasculature; 4) renal, hepatic, and splanchnic flow has been observed to decrease in severe heat stress at rest (by some, as

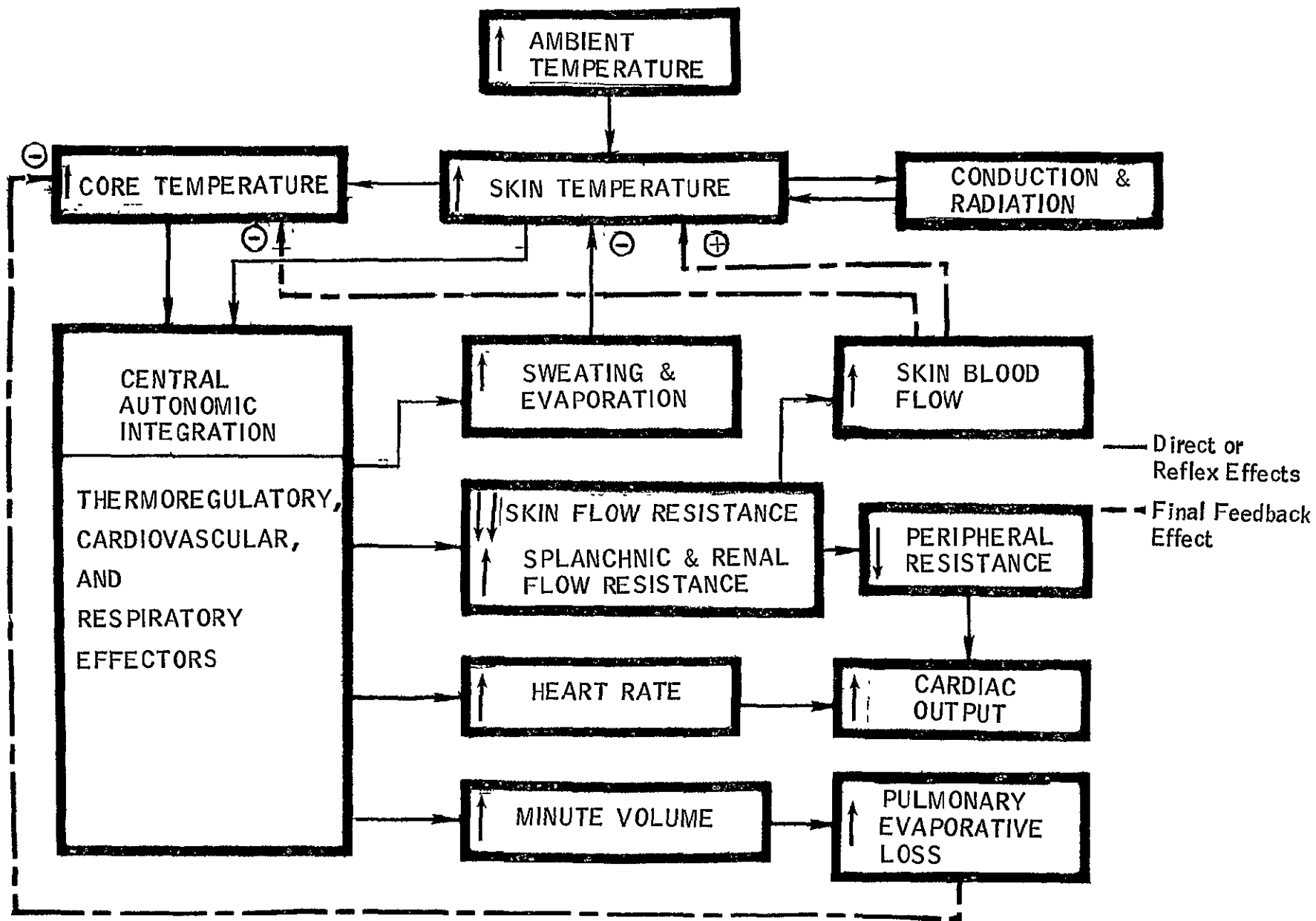


FIGURE 4-8 INTEGRATIVE PHYSIOLOGICAL REGULATION OF THERMAL STRESS AT REST

yet, unknown mechanism) while skin flow increases (Rowell, 1970). This readjustment of arteriolar resistance elements results in a decreased peripheral resistance; 5) heart rate increases have been observed to increase gradually with increasing body temperatures, probably resulting from autonomic stimulation from the thermoregulating centers. This effect on the heart, together with the decrease in peripheral resistance results in an increase in cardiac output by as much as 80% (Thauer, 1962; Wyss, 1974). No dramatic changes in stroke volume (or blood pressure) have been seen in spite of a tendency for increased myocardial contractility (Rowell, 1969); 6) the major response of the respiratory system is an increase in minute volume. Whether or not this is a direct temperature effect is not known, but the effect is gradual and mild until deep body temperatures are increased over $1 - 1.5^{\circ}\text{C}$ from the normal value, where marked increases have been demonstrated (Saxton, 1975). The net effect of the overall thermoregulatory system is so effective that during rest the core temperature is unlikely to rise more than a degree centigrade when ambient temperatures are increased by 30°C (Stolwijk and Hardy, 1966).

Simulation of Thermal Stress with the Whole-Body Algorithm

The thermoregulatory subsystem model contained the major thermoregulatory elements even before it was integrated into the whole-body algorithm and it was capable of accurate and detailed simulation of thermal stress in resting man. For example, it contained elements for conduction, radiation, sweating, skin blood flow regulation, shivering, and insensible pulmonary water loss. However, except for skin blood flow, the cardiovascular segments of the stand-alone model were very crudely developed and it had no capability of simulating important cardiovascular parameters such as blood pressure, peripheral resistance, heart rate, stroke volume, etc. It was felt that the pulsatile

cardiovascular model, when joined with the thermoregulatory model would contribute this information, as well as improving the cardiovascular portion of the thermoregulatory subsystem. On the other hand, the thermoregulatory models description of skin blood flow regulation during heat stress was markedly superior to the formulation in the pulsatile cardiovascular model. As discussed above there are thermal effects on the cardiovascular system besides skin blood flow regulation, concerning resistance changes of visceral organs and thermal effects on the heart rate. Compared to the data available relating heart rate to deep body temperature (Wyss, et al, 1974; Saxton, 1975; Selkurt, 1971; Damato, et al, 1965). little information was available concerning blood flow redistribution in response to changes in ambient temperatures. Consequently, only the former effect has been introduced in this preliminary version of the whole-body algorithm. These and other changes have been described in detail in the previous section. The effect of temperature on ventilation has been omitted from the model because this does not become an important factor until ambient temperatures, well beyond those studied here, are reached (Saxton, 1975).

The simulation of an environmental thermal stress was accomplished by changing values of the ambient dry bulb input parameter. Wall temperatures, effecting the radiant elements of heat transfer was also adjusted to be equal to the dry bulb and the wet bulb temperature was set to correspond to a relative humidity of 35%.

Comparison of Whole-Body Algorithm Simulation of Thermal Stress with Available Data

No previous studies were available which report simultaneous responses of cardiovascular, thermoregulatory, and respiratory variables in man at rest under graded levels of ambient temperature. Apparently the greatest experimental effort has been placed on investigating

the thermoregulatory system directly (i. e. , measurements of body temperatures and heat losses); there are relatively few studies concerning circulatory and respiratory responses. No experimental technique has been devised to measure whole-body skin blood flow directly, although indirect measurements have been reported. The best available data for body temperatures and evaporative heat losses as a function of ambient temperature have been published by Pierce Foundation Laboratory, originators of the thermoregulatory model used in this study (Stolwijk and Hardy (1966), Hardy and Stolwijk (1966)). Of the limited number of cardiovascular studies located, the most complete set of measured parameters comes from Damato, et al (1968) in which only a small number of subjects were tested at each level of ambient temperature and in which, unfortunately, no body temperature measurements were made. Temperatures from 20^o C to 42^o C were chosen as a reasonable range for which to test the model. The responses of the model and human test subjects to this graded heat stress are shown in Figures 4-9 and 4-10.

It is apparent that the whole-body algorithm is predicting correct responses for a wide variety of variables in all major subsystems throughout the temperature range studied. Inflection points in the data where changes become more marked with increasing temperature (i. e. , skin temperature, heart rate, cardiac output) are reproduced by the model. Discrepancies with the data on an absolute basis (especially evaporative loss) can be explained in part by the fact that the resting metabolic rate of the model was 10 - 20% higher than the average experimental values, and in part by the fact that the stand-alone thermoregulatory model predicted higher values for evaporative losses than was shown experimentally. Previous work with the thermoregulatory model has shown that evaporative loss rates are particularly

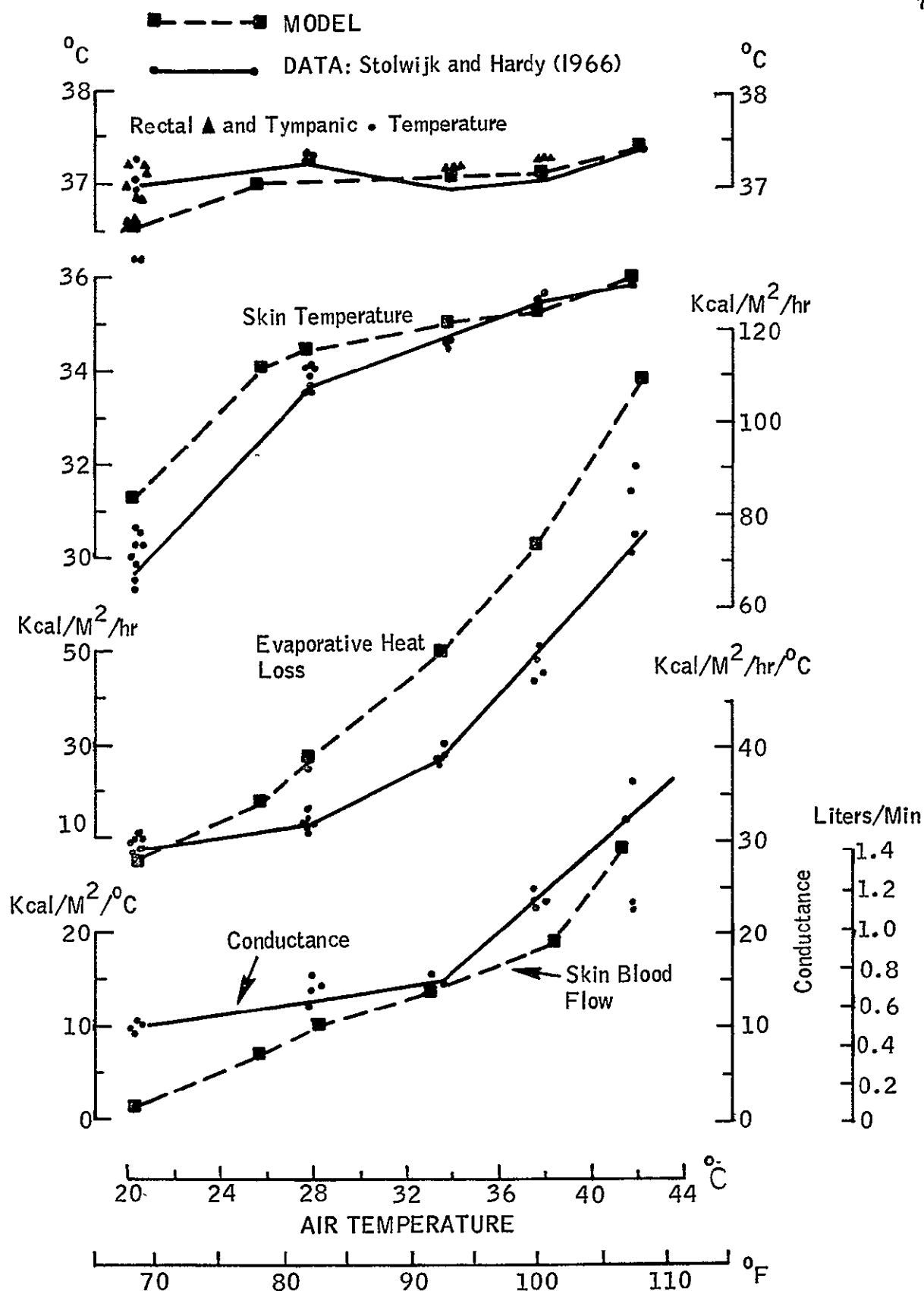


FIGURE 4-9 EFFECT OF ENVIRONMENTAL TEMPERATURE ON THERMOREGULATORY RESPONSE: MODEL VS. DATA

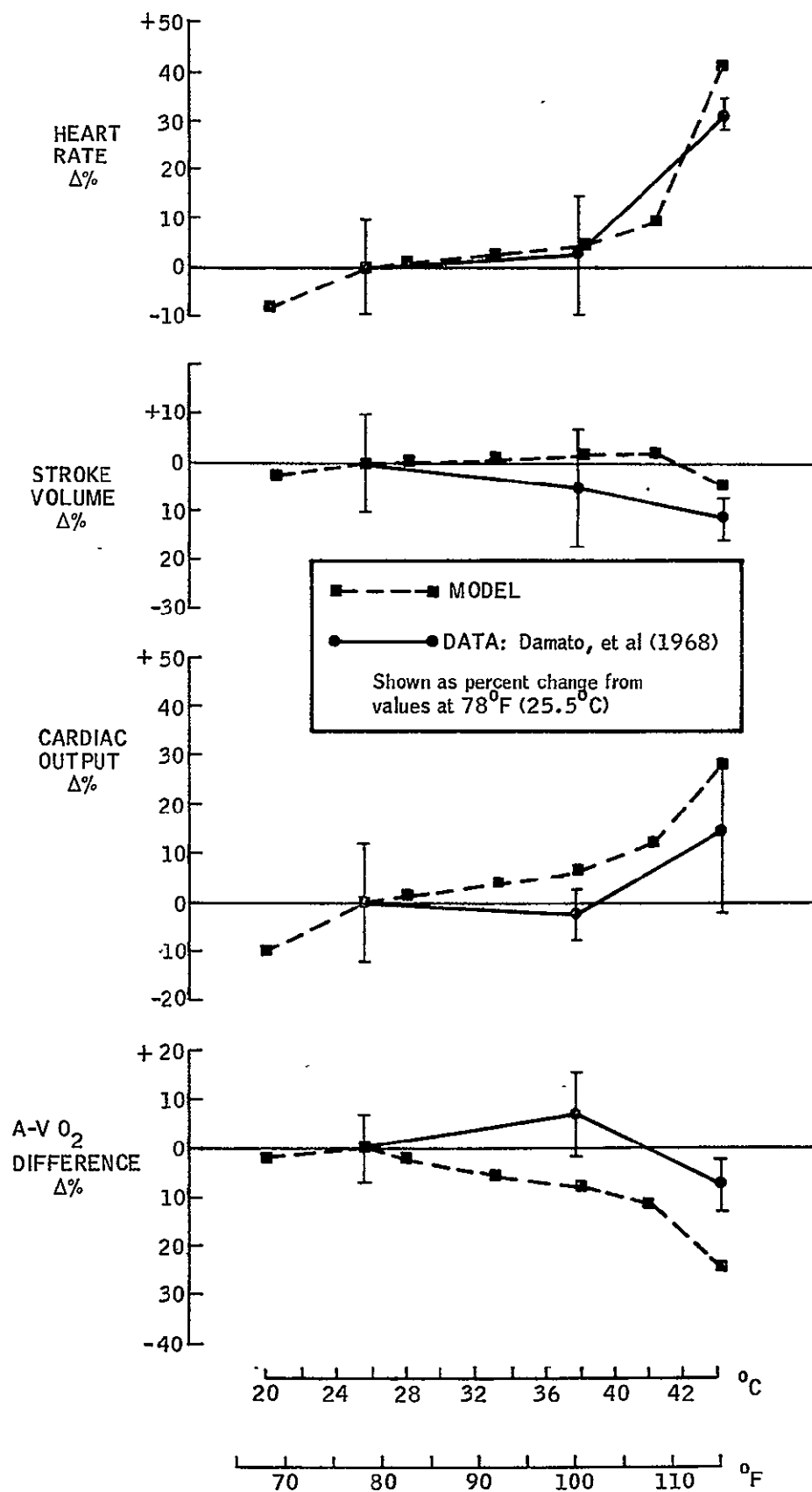


FIGURE 4-10 EFFECT OF ENVIRONMENTAL TEMPERATURE ON CARDIOVASCULAR RESPONSE MODEL VS. DATA

sensitive to the choice of metabolic rate. Unfortunately, it is not an easy task to change resting metabolic rates in the whole-body algorithm; its resting supine value, however, is in good agreement with many other sources.

The increasing stroke volume of the model is at variance with the decreasing values of the data although the divergence is small. This may reflect a decreased myocardial contractility or more probably a decreased central venous pressure in the human subjects as a result of temperature effects on venous tone. Neither of these effects have been introduced into the model. The decreasing A-V O_2 difference is a reflection of increased cardiac output being shunted mainly through the skin while oxygen uptake remained constant. Note that between 78° and 100° F the experimental cardiac output remained constant while in the model it increased slightly. The experimental findings might suggest that the increased skin blood flow at lower temperatures is effected by diverting blood flow from the internal organs while at higher temperatures the further demands on skin flow requires an increase in cardiac output (Damato, et al, 1968). This would suggest that the cardiovascular subsystem be modified to include this effect on the visceral organs. It is recommended, however, that any further modification be postponed until careful experiments can be performed that measure simultaneously the cardiovascular, thermoregulatory, and respiratory effects of graded thermal stress.

4.4 SIMULATION OF EXERCISE

Simulation of Bicycle Ergometry Exercise with the Whole-Body Algorithm

The understanding of exercise presents one of the most difficult and important challenges not only to physiological research but to modeling and simulation as well. Because exercise is essentially a

short term stress involving a complex interrelationship of metabolic, circulatory, respiratory, thermal, and neural activities (Astrand and Rodahl, 1970), it represents a perfectly suitable stress for severely testing the validity of the three major short term subsystem models. Each of these subsystems had the capability of simulating their respective subsystem responses to exercise prior to its incorporation into the whole-body algorithm. The assumptions upon which these models were based as well as examples of the individual model behavior have been described elsewhere. The links interfacing these subsystem models in the whole-body algorithm were designed to provide a more mechanistic and physiologically meaningful structure. For example, blood flows from the cardiovascular subsystem model were used to replace the gross, empirical description of the circulation contained in both the respiratory and thermoregulatory models. Also, the thermoregulatory model added appropriate elements to the cardiovascular subsystem, such as changes in skin blood flow, that previously did not exist. These interface links between subsystem models and other improvements to the individual subsystems have been described in detail in Section 3.0.

The chemoreceptor effect on the cardiovascular system and respiratory system, as well as the thermal receptor effect on heart rate are by-passed during the exercise simulation. These effects, which are known to exist during rest, do not appear to be significant during exercise in normal environments. The importance of these factors should be reevaluated if multiple stresses, such as exercise in hypoxic or hot environments, are to be considered.

Validation of the whole-body algorithm for exercise was accomplished by simulating bicycle ergometry in the sitting position for graded levels of exercise. The external work load is entered at the start of simulation as the only required forcing function. Only steady-state

responses are compared with experimental data since the published literature does not contain complete documentation of the transient response. In order to demonstrate the dynamic capability of the whole-body algorithm, two additional simulation runs are presented in this section for: a) a typical Skylab exercise protocol at intermediate work loads and b) a longer duration high metabolic load protocol.

Comparison of Exercise Simulation with Available Data

Figure 4-11 illustrates the behavior of some of the more important dependent variables of the whole-body algorithm during graded levels of exercise (Rest, 50 watts, 100 watts, 150 watts, and 200 watts). Comparison with experimental data from a single literature source (Ekblom, et al, 1968) is also shown. Both simulation and experimental values have been obtained after 5 minutes of exercise. Agreement is considered to be excellent and better in some respects than with the pulsatile cardiovascular model operating alone. The model was able to correctly predict a wide variety of hemodynamic and respiratory responses including steep linear changes (i. e. , heart rate and oxygen uptake) and highly nonlinear changes (i. e. , stroke volume, blood pressures, and ventilation rate) over a wide range of metabolic rates.

Compared to the cardio-respiratory system, the thermoregulatory processes require a much longer time to equilibrate or reach a quasi-steady-state. This is due to the high degree of thermal inertia of the body tissues. Dramatic changes were not seen by the end of these short term (5 minute) exercise studies in such variables as body temperature, sweat rates, and skin blood flows. These responses are not shown in this first series of exercise simulations, but the few reports available support the results that important thermoregulatory responses to exercise are not seen during the first few minutes (Saltin, et al, 1970).

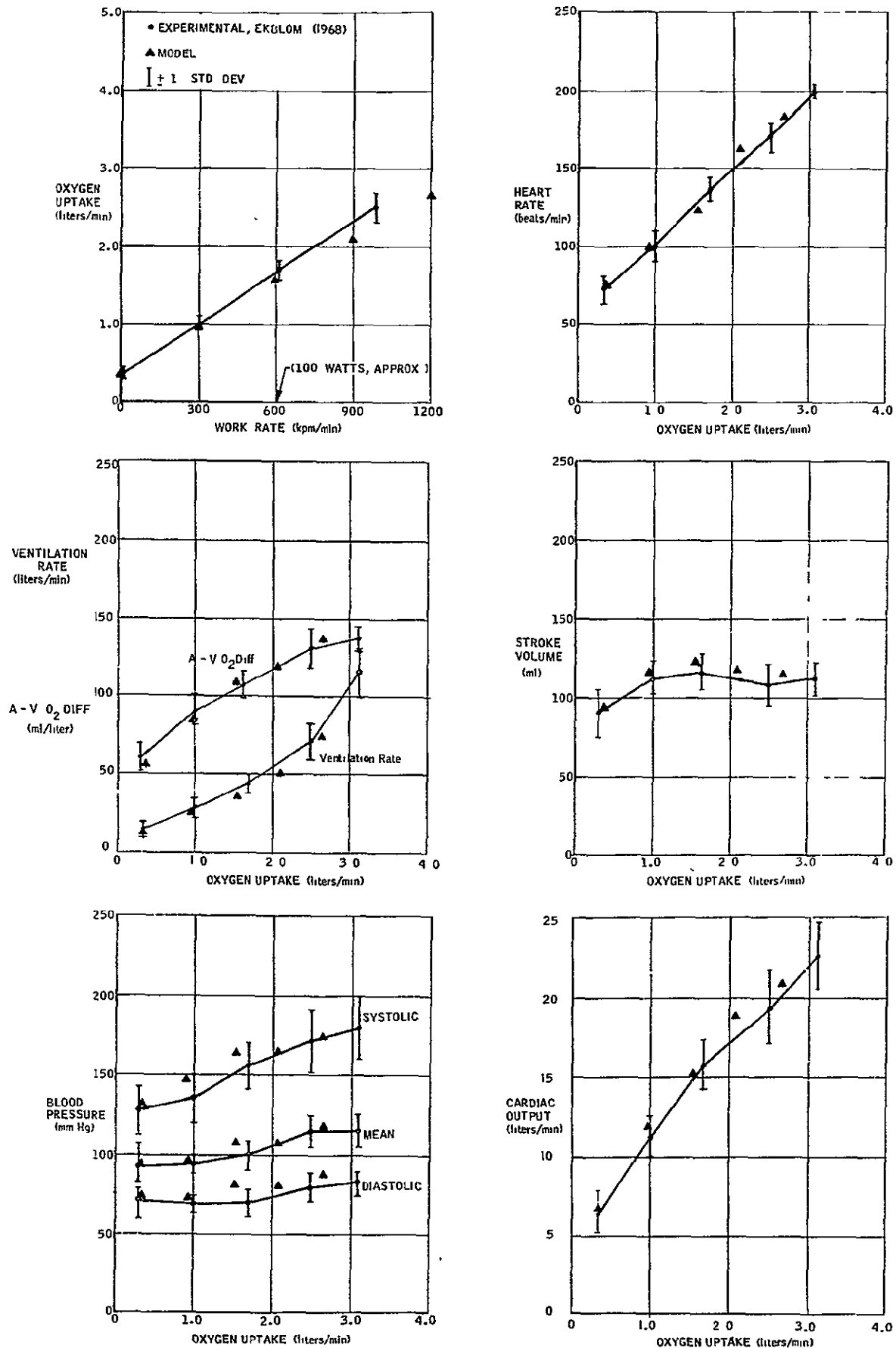


FIGURE 4-II EFFECT OF EXERCISE ON CARDIO-RESPIRATORY RESPONSE
MODEL VS DATA

In order to properly demonstrate the thermoregulatory capability of the whole-body algorithm during the stress of exercise and to illustrate the model's capability to produce time-dependent responses, two additional simulations were made.

In the first of these (Figure 4-12) a typical Skylab type exercise protocol was simulated consisting of five minute sequences of three graded levels of exercise, 50 watts, 100 watts, and 150 watts followed by a recovery period. Responses from all three short term subsystem models are shown and all, except heat storage rate and body temperature tend toward steady-state values at the end of each five minute exercise segment. It also should be observed that no dramatic changes are predicted to occur for arterial pO_2 and pCO_2 during exercise except for the on-transient. This is supportive of many physiological observations and illustrates the current dilemma of respiratory physiologists to explain the dramatic hyperpnea of exercise in spite of these small changes in gas tensions. The behavior of the recovery simulation appears to be reasonable for most of the variables illustrated (i.e., O_2 uptake, cardiac output, heart rate, etc.). However, while the transient changes observed for blood pressure, blood gas tensions, and evaporative loss appear to be questionable, time did not permit a complete evaluation of the causes of these responses or to find supportive or conflicting experimental data. The off-transient to exercise, especially the integrated response shown here, has not been well studied. However, a recent report from Linnarsson (1974) does suggest that some of these unexpected responses may be supported by his investigation, but further study is certainly indicated in this area.

While many of the cardio-respiratory responses appear to have reached new steady-state levels in relatively brief periods of exercise, this effect is more apparent than real. The continual production of metabolic heat cannot permit body temperature to equilibrate until the

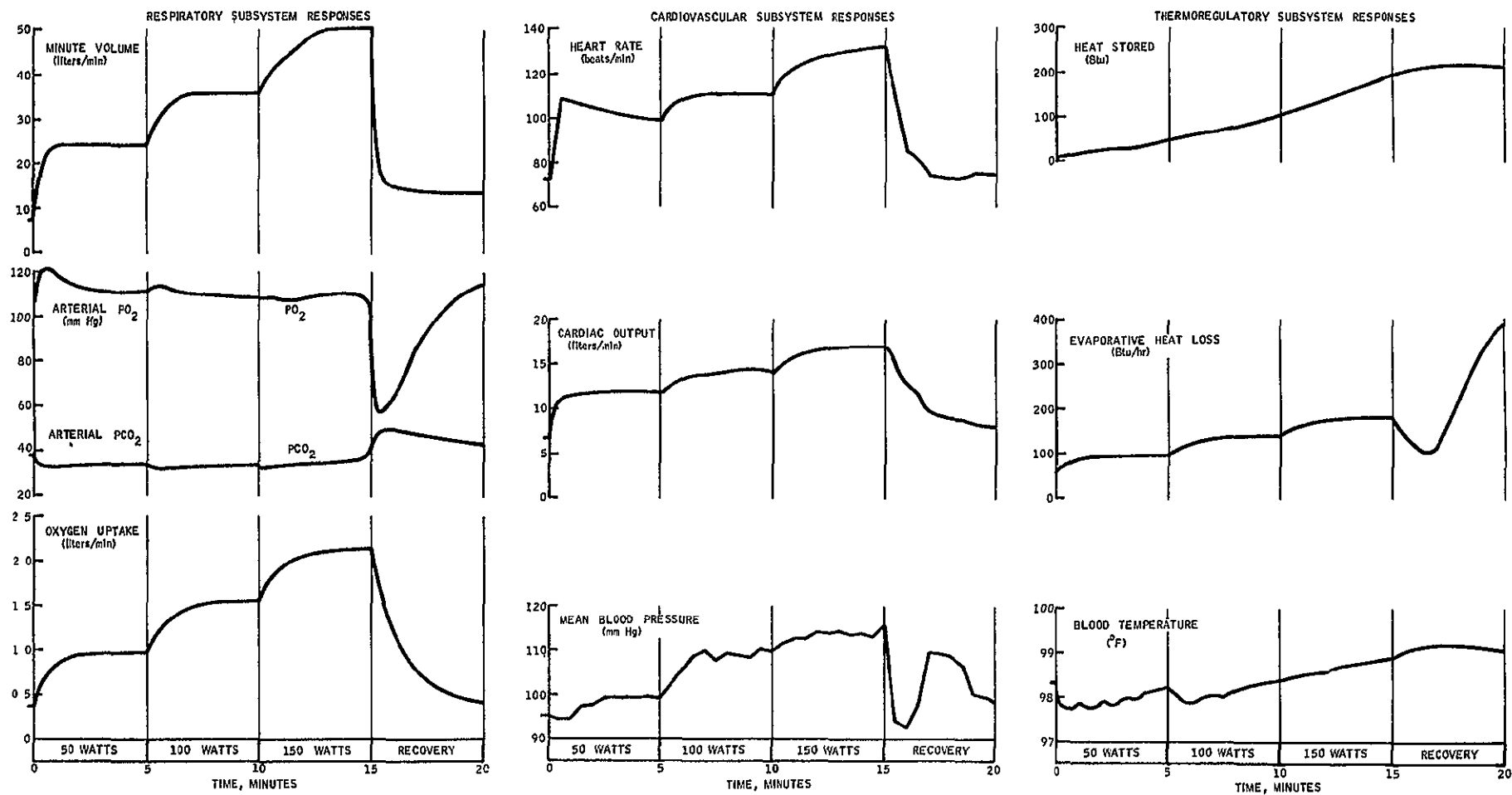


FIGURE 4-12 SIMULTANEOUS RESPONSES FROM THE WHOLE BODY ALGORITHM SIMULATING A SEQUENTIAL EXERCISE PROTOCOL OF 50, 100, 150 WATTS AND RECOVERY

thermoregulatory processes have been completely activated. This process can take much longer than the time simulated in these simulations. Skin blood flow (not shown) has not begun to increase at the end of this sequence and evaporative losses are only a small fraction of their final steady-state values. Thus, if exercise had been allowed to continue for a longer period, changes would be expected in those responses of the thermoregulatory subsystem model which are dependent on heat production (i. e., body temperatures, sweating, skin blood flow), as well as in variables of the cardio-respiratory subsystems that are dependent on skin blood flow (i. e., cardiac output, A-V O_2 difference, peripheral resistance and blood pressure). This is shown more clearly in the next example.

The capability of the whole-body algorithm to predict dramatic changes in thermoregulatory responses to a longer and more severe exercise bout (200 watts for 30 minutes) is shown in Figure 4-13(a). While there are few examples in the literature with which to compare these predictions of transient behavior, Saltin, et al (1970) has reported similar results for three subjects, only one of which was presented in detail and is reproduced in Figure 4-13(b). (It should be noted that some conditions of the experiment were not represented precisely in the simulation: the more important differences included the air temperature (20°C in the experiment and 24°C in the simulation), body surface area (2.09 m^2 vs. 1.8 m^2), maximum heart rate (235 beats/min vs. 200) and steady-state oxygen consumption during exercise (3.15 liters/min vs. 2.75)).

Both simulation and experiment show similar changes in body temperatures. The esophageal temperature of the subject and blood temperature of the model (both representing deep body temperature) rose approximately 1.5°C while the skin temperature changes were about twice as great over the 30 minutes of exercise. The simulated skin blood flow shows a steep rise similar to the experimentally determined thermal conductance (a crude estimate of skin flow). Maximum

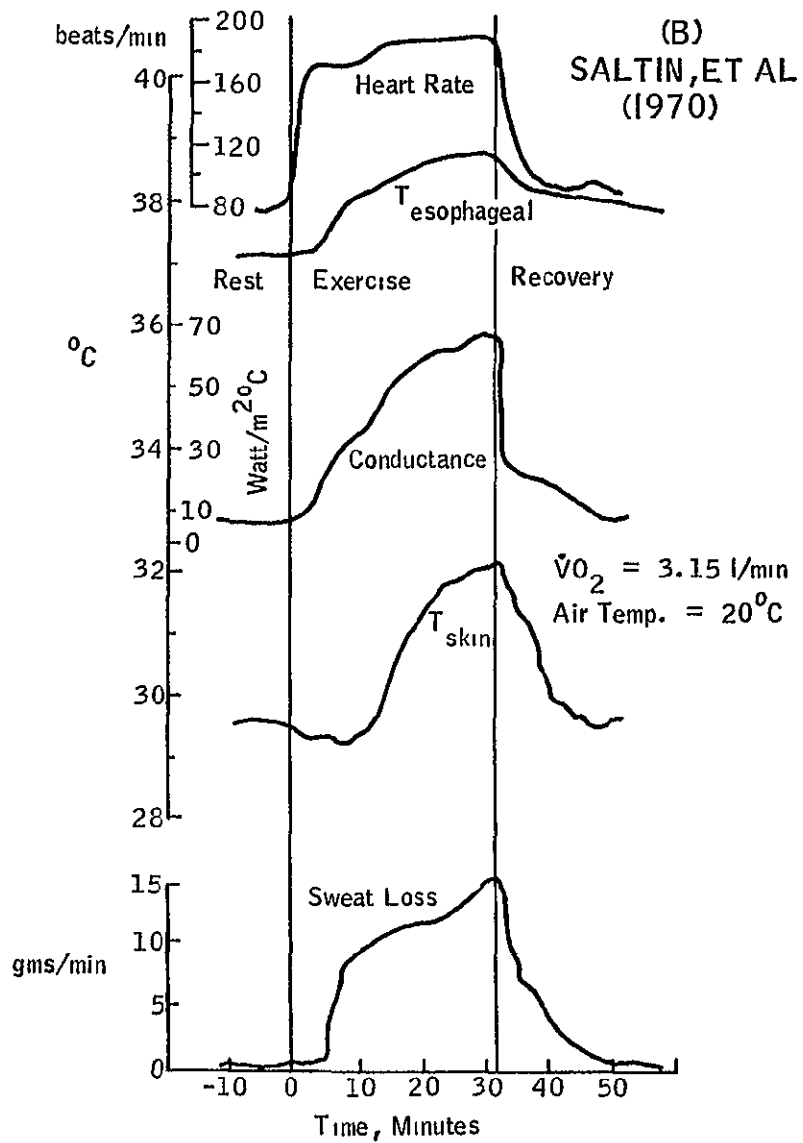
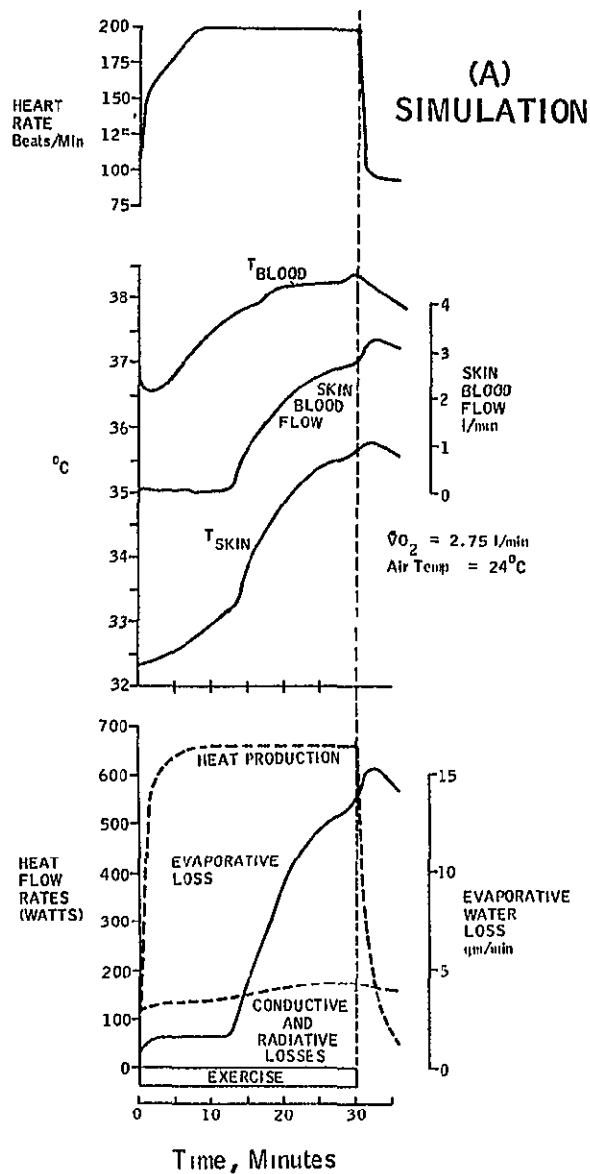


FIGURE 4-13. TRANSIENT RESPONSE TO 200 WATT EXERCISE: MODEL VS DATA

sweat rate of the human subject was about 15 gms/min, a value predicted by the model. While the model's transient response during the onset and recovery of exercise could be improved, it is noted that significant delays in the rapid onset of deep body temperature, skin temperature and sweating rates are shown in both the human experiment and the simulation. Conductance may not be a true measure of skin blood flow during exercise since it is affected by muscle blood flow as well. Therefore, it would be expected that the delay in skin flow predicted by the model might not be revealed by this indicator. More recent studies have demonstrated a significant delay in skin flow during the onset of exercise (Johnson, et al, 1974; Wenger, et al, 1975).

Also shown in Figure 4-13(a) are the predicted behavior of conductive and radiative losses (known to remain relatively constant) and rate of heat production. In the model, 78% of the energy produced during exercise is converted to heat within the body and the rise in heat production to steady-state parallels the dynamic behavior of oxygen uptake as well as muscle blood-flow. Prior to its incorporation into the whole-body algorithm, the thermoregulatory model did not have the capability of accurately simulating the onset of muscle blood flow or heat production; flow increased immediately to a value determined by the work load. It was suspected that a better representation of circulatory factors would improve the simulation of convective transport of heat in the body and minimize the transient drop in deep body temperature during the first several minutes of exercise. This phenomena, shown for T_{blood} in Figure 4-13(a), ultimately effects the entire thermoregulatory response and helps account for the excessive delay in activating these processes. The fact that these hoped-for improvements have not occurred in these simulations of the whole-body algorithm, which contains a more accurate representation of blood circulation, leads one to suspect that other important factors have not been accounted for.

As previously mentioned, the activation of thermoregulatory elements, particular skin blood flow, would have effects on the entire cardiovascular system that would only become apparent after prolonged exercise. If the onset of skin blood flow increase were used as a point of reference, ($t = 12$ minutes), changes obtained during the simulation of Figure 4-13(a) between this reference point and the end of 30 minutes of exercise were found to include: a 7 % increase in cardiac output, a 6% decrease in mean blood pressure, and a 17% decrease in A-V O_2 difference. While no data could be located to confirm these predictions for long term exercise, it is apparent that the extra demands of blood flow to the skin has resulted in a greater cardiac pumping requirement and a decrease in peripheral resistance, but more significantly, this simulation has shown why a true physiological steady-state may not be obtainable after five minutes of severe exercise (Ekelund and Holmgren, 1964).

Other hypothesis can be easily tested in the whole-body algorithm. For example, the exercise recovery response may be improved by introducing an observed effect on sweating related to the rate of decrease in body temperature (Wyss, et al, 1974). Also, certain investigators believe that the sweating response to exercise is more due to the rate of heat production than to skin and deep body temperature, the latter mechanism being used in the model (Astrand and Rodahl, 1970). Comparison of the responses in Figure 4-13 certainly suggests that this is not true during the early minutes of exercise.

In summary, while we have not attempted to make a quantitative comparison between the stand-alone models' responses to exercise and the response of the whole-body algorithm, it has become apparent that the whole-body algorithm simulation is superior in many respects. This is true with regard to accuracy of response, stability, and in particular, the

ability to predict detailed simultaneous responses from several important physiological systems involved in the exercise stress. Although still untested, the capability now exists to combine multiple environmental and metabolic stresses for studying some very important physiological conditions such as supine or sitting exercise in environments of abnormal pressures, temperatures, humidities, and gas concentrations as well as studying the effects of such important parameters as blood volume and hemoglobin concentrations.

4.5 SIMULATION OF PROLONGED BED REST FOLLOWED BY TILT AND EXERCISE

Physiological Response to Long Term Bed Rest

In the supine position of bed rest, the hydrostatic effects produced by gravity acting upon the columns of blood, are greatly reduced. This results in a shift of blood, mostly from the legs, to the central vascular segments, primarily in the thorax (McCally and Graveline, 1963). This apparently simple stress of assuming the supine position initiates a chain of events that are characterized by changes in body fluid volumes, blood flows, electrolyte and urine excretions, thirst, and hormonal release. (Murray and McCally, 1971; Fuller, et al, 1970; Vogt and Johnson, 1967; Piemme, 1968; Deitrick, et al, 1948; McCally, et al, 1971). Most of the more dramatic changes occur rather rapidly, within one to three days. Prolonged bed rest for several weeks appear to reverse some, but not all of these effects. Undoubtedly, the inactivity that accompanies bed rest, can account for other changes that are observed such as muscle atrophy, calcium loss, increased potassium excretion and weight loss. Stressing the cardio-respiratory system following bed rest by such techniques as the tilt-table, LBNP, or exercise results in orthostatic intolerance and decreased maximum exercise performance (Hyatt, 1968; Saltin, et al, 1968).

Studies on bed rest have been of significant interest in recent years because of its relationship to the weightlessness of space flight. The weightless state is quite analogous to bed rest with respect to the absence of the hydrostatic forces acting on a fluid column and their effect on hydrostatic dependent physiological systems (McCally and Graveline, 1963). Indeed, many but not all of the same changes seen in post-bed rest studies are also seen in crews returning from space and the recently completed Skylab medical experiments have suggested that many changes during space flight are strikingly similar to those occurring during bed rest (Johnston and Dietlein, 1974). Immersing a subject in water is another technique that reduces the hydrostatic effects on the fluid column and tissues, and it has been demonstrated that the physiological changes accompanying this stress are qualitatively similar to many of those seen in short term bed rest including the post-bed rest "deconditioning" phenomena (Epstein, 1974; Arborelius, et al, 1972; Gauer, 1971; Stegmann, et al, 1975). The degree of correspondence between bed rest, immersion, and weightlessness is a subject of current study. Nevertheless, the potential applicability of this analogy in helping to elucidate possible physiological mechanisms occurring in weightlessness coupled with the fact that a large collection of bed rest data are currently available has prompted this preliminary study of bed rest simulation utilizing the whole-body algorithm.

The model of Dr. Guyton that is included in the whole-body algorithm was expressly formulated for simulating long term physiological changes in the body concerned with circulatory, fluid and electrolyte regulation. The model has been tested in Dr. Guyton's laboratory and validated for many specific clinical and experimental conditions such as renal hypertension induced by salt loading and renal deficiency, congestive heart failure, nephrosis, infusions of solutions, and severe muscle exercise (Guyton, et al, 1972). Reasonably accurate simulations have been

obtained in these cases for simulated times that range from minutes to several weeks. Inasmuch as many of the changes accompanying prolonged bed rest occur in the systems represented in this model, it was felt that a bed rest simulation would present an appropriate and relevant challenge to the long term model. Further, since the short term model subsystems of the whole-body algorithm are capable of simulating LBNP, tilt, and exercise tests that have been performed before and after bed rest, a combination of long term bed rest and short term stress simulation would be an eminently suitable validation test for the entire whole-body algorithm. There are no precedents to this simulation, and only a very short amount of time was available for the investigation. For this reason, the results should be considered quite preliminary.

No complete description of the physiological response to bed rest or immersion can be provided in spite of the large number of experimental studies. For example, the exact mechanisms underlying the early diuresis often observed during bed rest and immersion have not been clarified (Gauer, 1971). Also lacking is an adequate explanation for the decrease in red cell mass which is often reported (Johnson, et al, 1971). The emphasis of this simulation will be on describing body fluid distribution with its accompanying changes in circulatory dynamics, major electrolyte changes, renal hemodynamics, and some related hormonal changes. Many other changes ~~that~~ are known to occur such as muscle atrophy, calcium loss, and changes in acid-base balance cannot be considered at present.

Simulation of Bed Rest and Immersion with the Whole-Body Algorithm

At the outset of this study an important question had to be addressed. What physiologically acceptable stimulus or forcing function would cause the long term model to simulate the reduction in hydrostatic effect that accompnies bed rest? The long term model does not contain gravity dependent systems and to introduce this effect would be a considerable task. The solution to this apparent

dilemma was resolved by noting that the primary event accompanying a reduced hydrostatic effect is a shift of blood from the legs to the central regions of the vasculature. The resulting increase in blood pressures in this region coupled with the fact that this area of the vasculature contains the major low and high pressure sensors of the body is generally believed to be the causal factor for many of the physiological changes to follow. However, the long term model did not have a separate leg compartment represented from which to shift this fluid. It was eventually decided that a reasonable approximation to the fluid shift phenomena could be obtained by shifting blood from the unstressed blood volume to the stressed blood volume. In general, if the central blood volume of the body is equal to the unstressed blood volume, then essentially no pressure will be exerted on the pressure receptors. This means that only changes in the stressed blood volume (which is a small fraction of the total blood volume) initiate pressure receptor effects. The volume of fluid shifted would be approximately the same amount that has been observed to be displaced from the legs when changing from the erect to supine posture (about 300 ml). The fact that the unstressed volume has been reduced is of no consequence since it contributes nothing toward changes in pressures. Only the total blood volume and the stressed volume are the crucial factors affecting pressures, plasma concentrations and other aspects of fluid-electrolyte regulation. In this method of simulation total blood volume remains constant while the step change in stressed volume takes place. In a model without a leg compartment it is impossible to simulate events in the legs (such as postulated compliance changes, tissue dehydration, reverse stress relaxation), but it is believed that these factors do not assume importance until a subject returns to the upright position. The small amount of reprogramming necessary to accomplish this step change of 300 ml shifted to the stressed volume is described in Section 3.0.

Only one other change was made to the structural elements of the long term model to simulate bed rest, which was the addition of a function that increased the heart rate at 0.4 beats/min for each day of bed rest. Abundant bed rest data from different studies suggest this

cardiovascular effect, although no mechanisms have been elucidated, (i.e., Birkhead, 1963). Simulations were run with and without this effect and except for increasing heart rate and decreasing stroke volume changes, there were no other differences in behavior of any other variable including cardiac output.

Before and after simulated bed rest with the long term model, an additional series of stresses were automatically performed utilizing the short term subsystem models to simulate 70° tilt and 50 watt supine exercise. In experimental studies, these tests helped to reveal physiological changes that occurred during bed rest that were not always apparent in the supine resting state. Interfacing links between the long and short term models, already described would initialize the short term models at the end of bed rest depending upon the changed state of the long term model.

Comparison of Bed Rest Simulation with Available Data

Results of a 28-day bed rest simulation are shown in Figure 4-14. The simulation revealed that many new quasi- steady-state conditions were reached at the end of four simulated weeks and that 90% of these changes had occurred by the end of the first day. Therefore, the model's behavior is shown in more detail for the first 24 hours. Only 24 of the more than 350 variables of the long term model are shown because of the limited number of experimental variables available for comparison. These experimental results from bed rest are shown in Figures 4-15 to 4-19. Data from water immersion and postural change studies are included because of the analogies already discussed. More importantly, if an analogy does exist between these phenomena, immersion and postural change studies provide insight into the important short term changes that occur in bed rest. As a rule, bed rest investigators fail to measure physiological variables during the first few critical hours. Thus, in the data used, postural change studies (tilting from supine to erect or visa versa), water immersion studies and bed rest studies provide data for the first hour, first six hours, and up to 7 weeks,

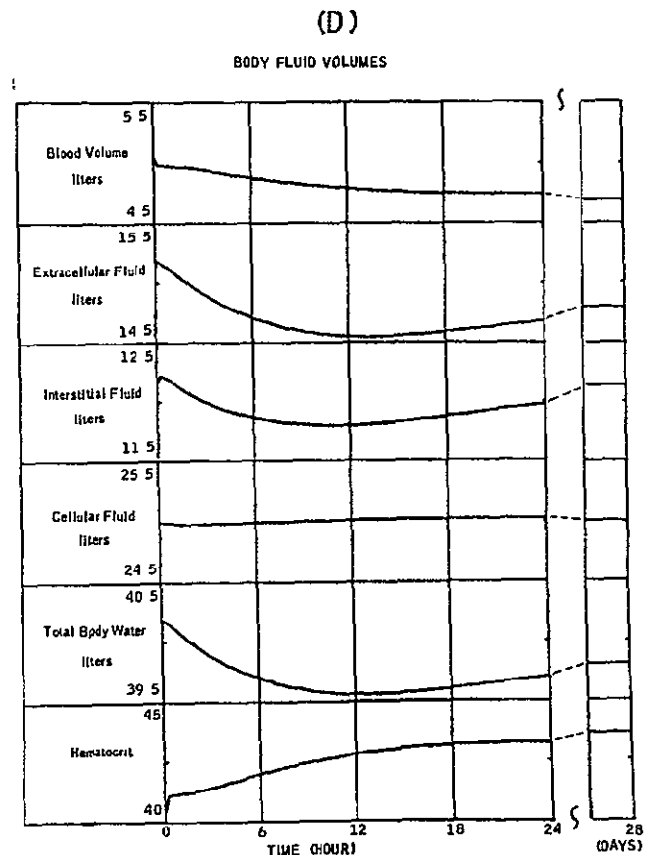
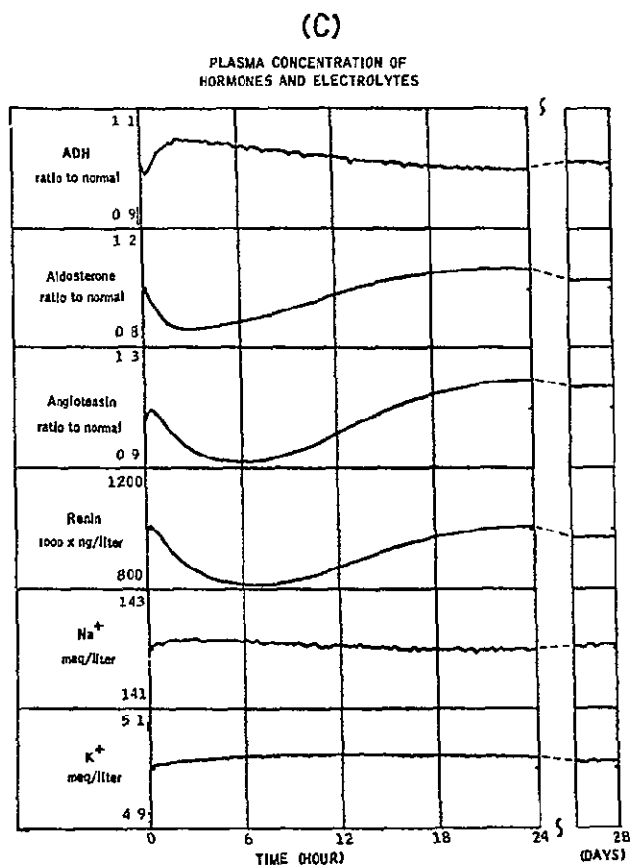
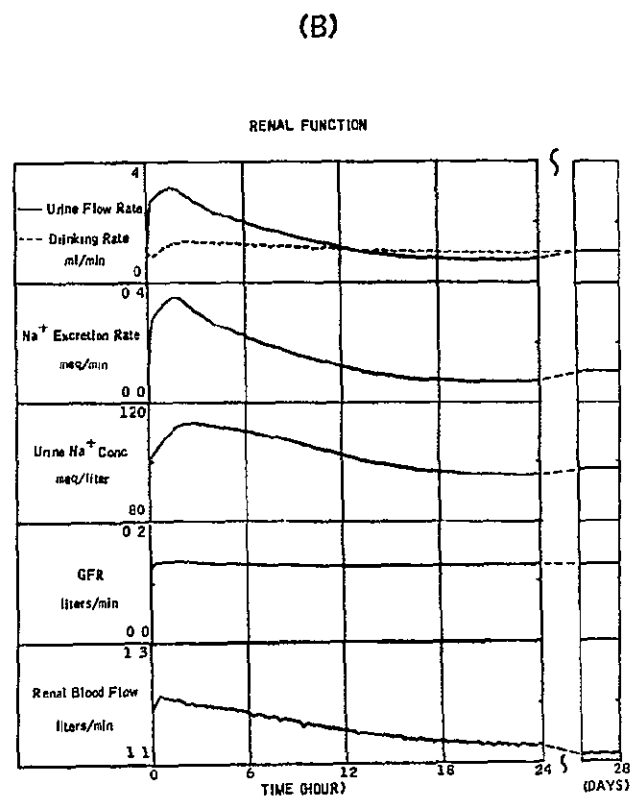
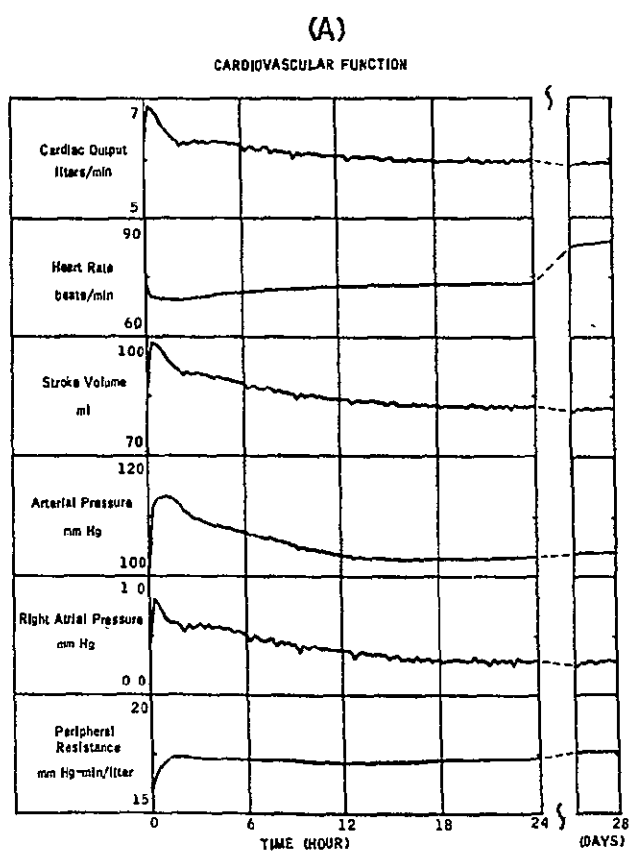


FIGURE 4-14 SIMULATED RESPONSES TO 28 DAYS OF BED REST

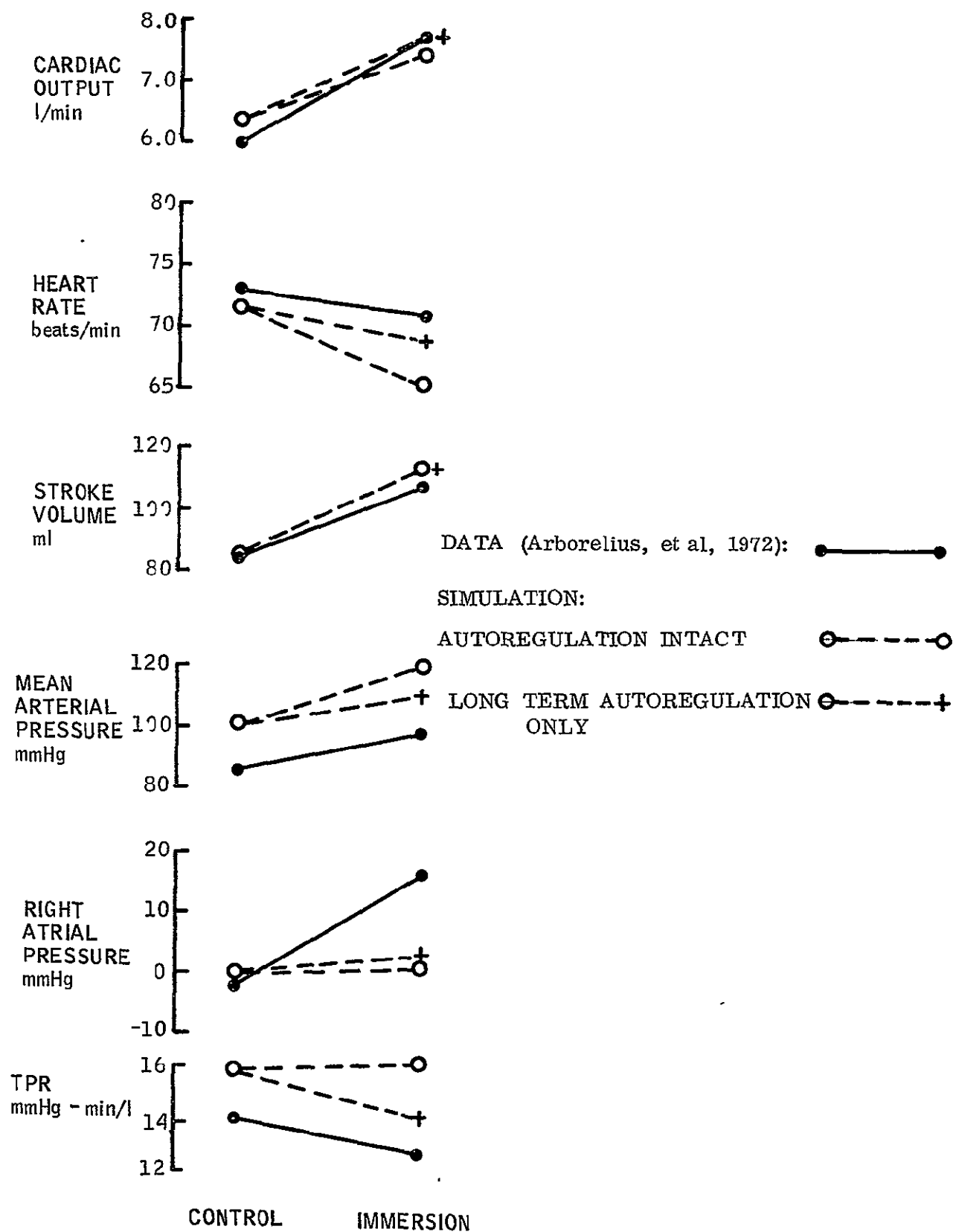


FIGURE 4-15 HEMODYNAMIC RESPONSE TO 10 MINUTES IMMERSION:
MODEL VS DATA

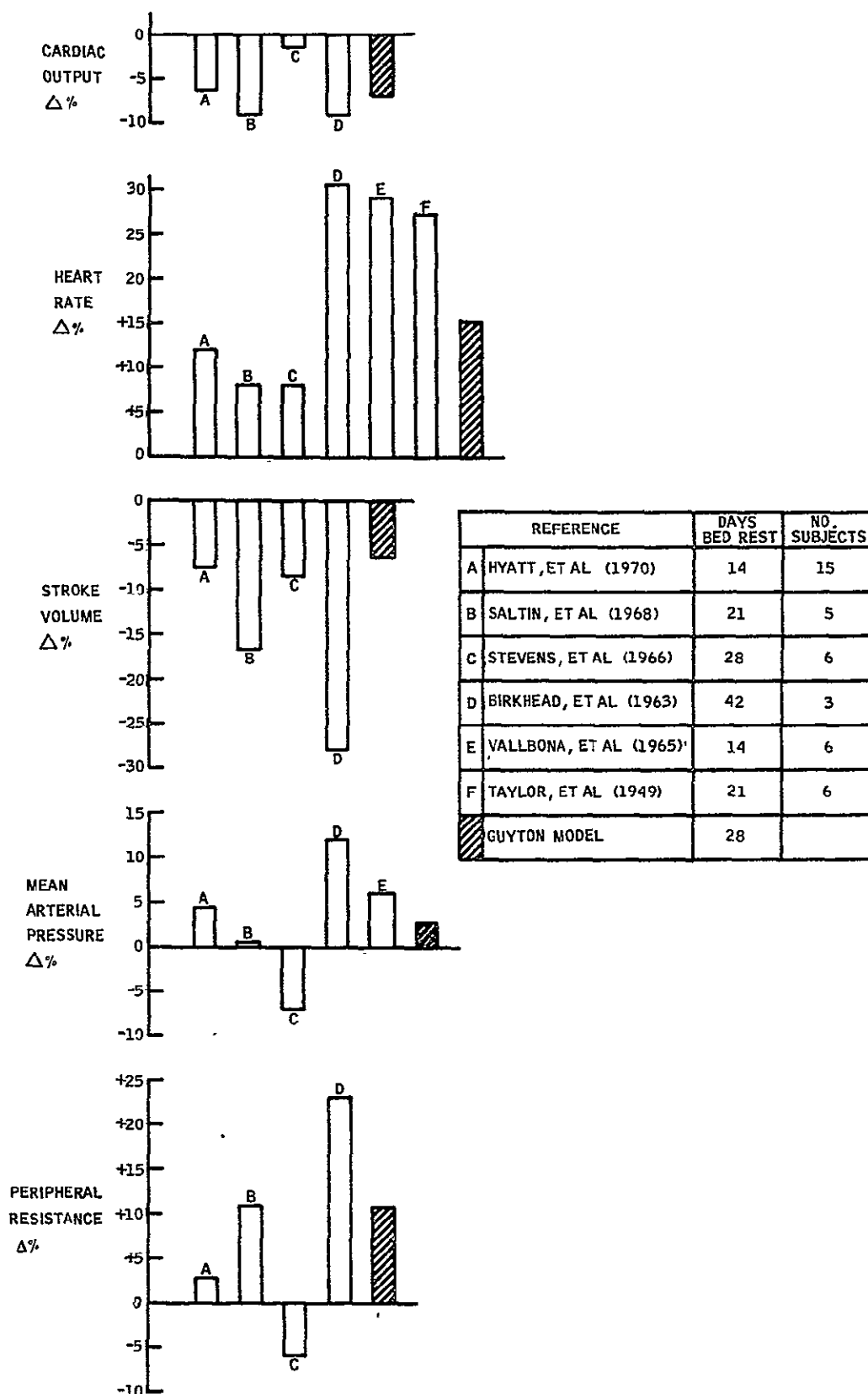
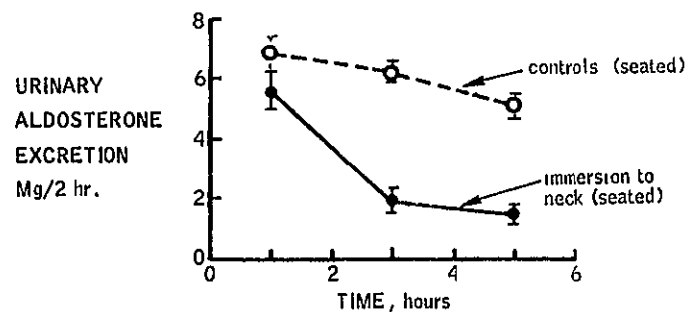
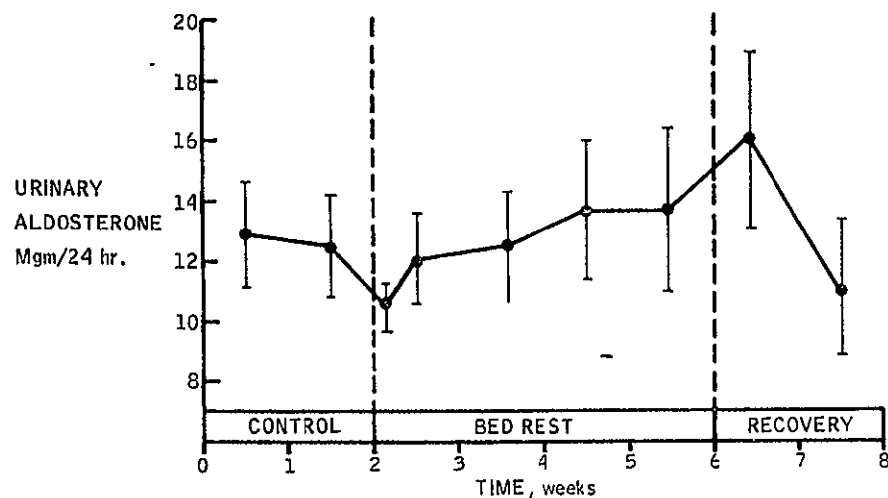


FIGURE 4 - 16 PERCENT CHANGE OF HEMODYNAMIC RESPONSE
DUE TO PROLONGED BED REST
MODEL VS DATA

(A)
EXPERIMENTAL ALDOSTERONE RESPONSE TO SHORT TERM
IMMERSION AND LONG TERM BED REST

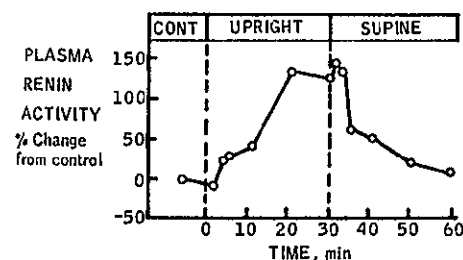


Urinary Aldosterone Response to Immersion
in Subjects on Low Sodium Diet
(Epstein and Saruta, 1971)

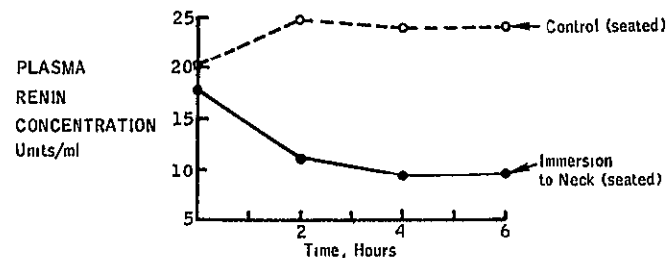


Urinary Aldosterone Response To Four Weeks
Bed Rest in Normal Subjects
(Hyatt, et al 1970)

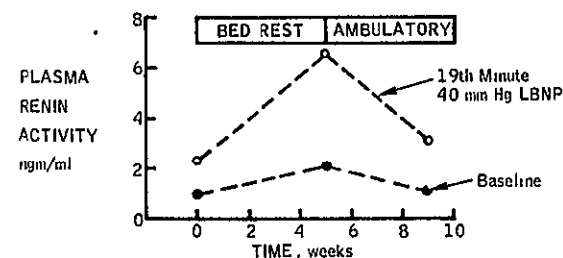
(B)
EXPERIMENTAL RENIN RESPONSE TO SHORT TERM POSTURAL CHANGE,
INTERMEDIATE-TERM IMMERSION AND LONG TERM BED REST



Renin Response to Short Term Postural Change
on Tilt Table (Haber, 1971)



Renin Response to Immersion in Subjects
on Low Sodium Diet (Epstein and Saruta, 1971)



Renin Response To Five Weeks Bed Rest
and During LBNP (Fasola, et al 1970)

FIGURE 4-17 EFFECT OF POSTURAL CHANGE, IMMERSION AND BED REST
ON ALDOSTERONE (A) AND RENIN (B) RESPONSES

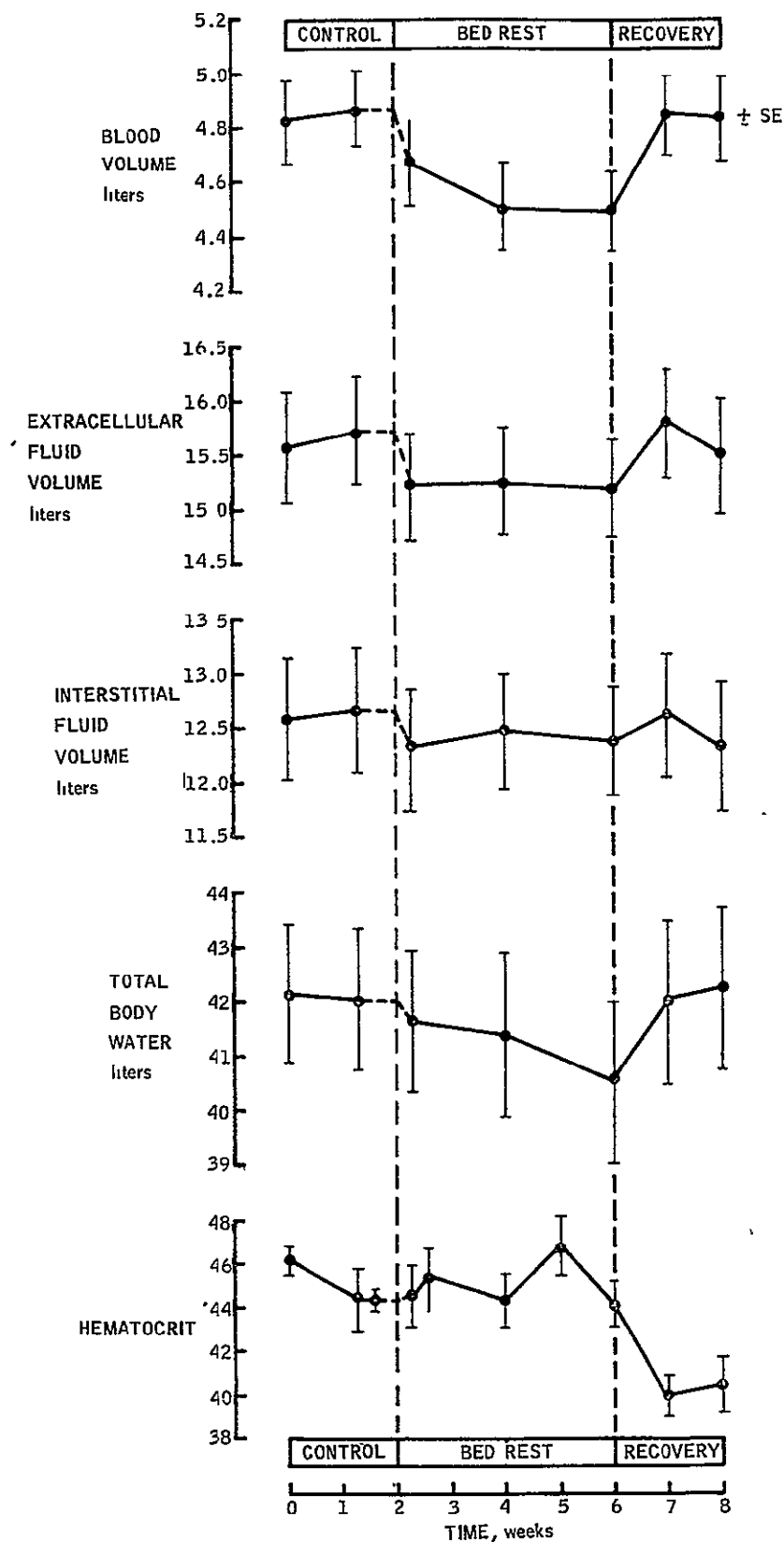


FIGURE 4-18 BODY FLUID VOLUME CHANGES DURING FOUR WEEK BED REST (HYATT, ET AL, (1970)

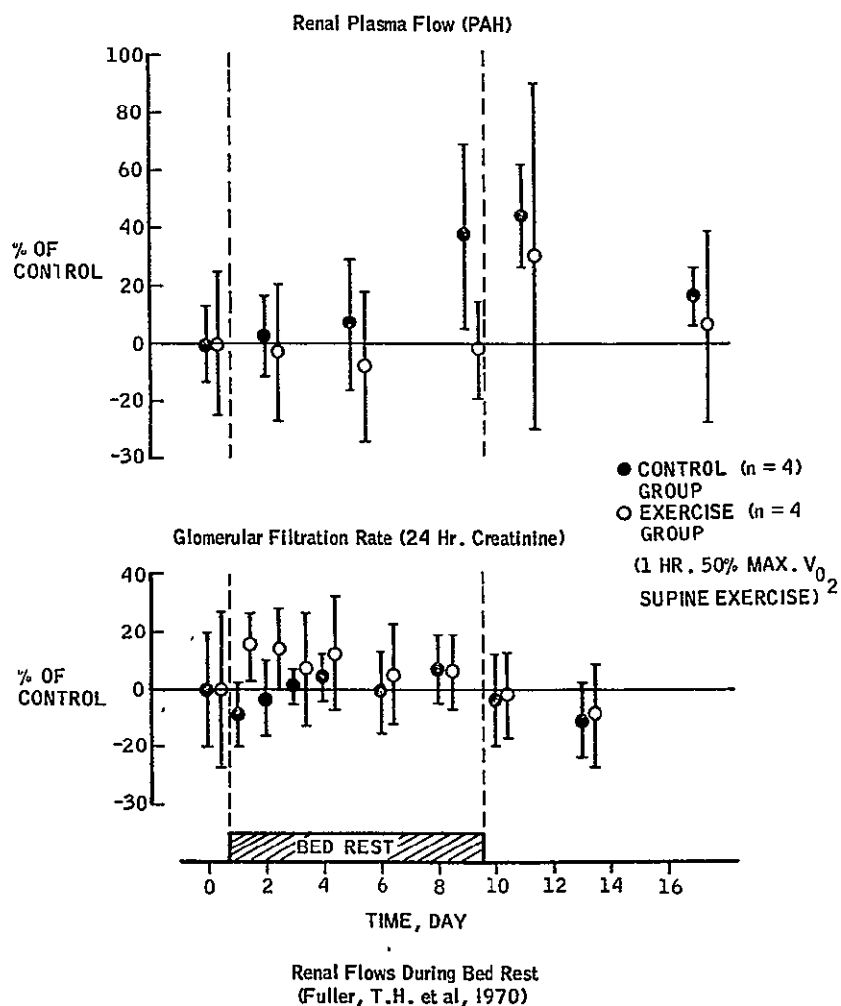
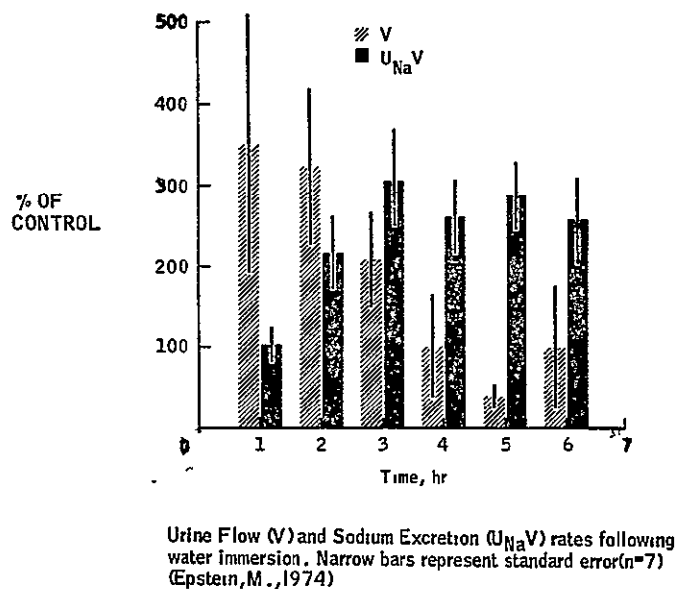


FIGURE 4-19 RENAL FUNCTION DURING WATER IMMERSION AND BED REST

respectively, following a reduction in hydrostatic pressure effects. This is only approximately correct since immersion and bed rest minimize hydrostatic effects to different degrees.

It is apparent from the simulation and the data presented that the adjustments to changes in gravitational stress are quite rapid. Within the first few simulated minutes the blood pressures in both arterial and atrial segments rise causing increases in stroke volume and cardiac output (Figure 4-14(a)). Heart rate reflexly decreases due to baroreceptor influence. As a result of the rapid rise in blood pressures, the urine flow rate and sodium increases (Figure 4-14(b)) primarily as a result of a transient decline in aldosterone (Figure 4-14(c)). The increase in urinary fluid loss leads to decreases in blood volume, extracellular fluid volume and total body water as well as vascular hemoconcentration (Figure 4-14(d)). Hormonal plasma concentrations also are changed as a result of these changes in central blood volume. ADH is shown to decrease only for the first half hour and then transiently rise. Transient decreases in aldosterone, angiotension, and renin are predicted while sodium and potassium plasma concentration remain essentially unchanged. Many of these variables are not predicted to return to their pre-bed rest values at the end of 28 days, the most notable of these being: blood volume, extracellular fluid, total body water, hematocrit, cardiac output, heart rate and stroke volume, blood pressures, peripheral resistance, renal flow, angiotension and aldosterone. Most of these effects have been observed during bed rest and immersion studies.

Comparison of the simulated hemodynamic changes at the 10-minute mark is made in Figure 4-15 with data taken 10 minutes after water immersion. In the simulations shown on this figure, the blood volume shift from unstressed to stressed compartments was 700 ml, rather than the 300 ml used in all other comparisons in this study. This is in agreement with the 700 ml increase in central blood volume measured at 10 minutes by the investigators of that study. The open circles represent a normal simulation and agreement with data is good except for right atrial pressure, which is less than the data, and for

TPR which shows an increase rather than a decrease. The large experimental change in right atrial pressure is almost certainly due to the hydrostatic effect of the water compressing the thoracic cavity, a factor not included in the model. However, the discrepancy with peripheral resistance is more disturbing. Upon further investigation of the model's performance, it was found that the baroreceptor influence was indeed acting correctly in attempting to suppress TPR following the stress, but this influence was being overwhelmed by a blood flow autoregulation effect which acts to bring flows through the individual tissue bed back to normal following a flow disturbance. Autoregulation consisted of short term, intermediate term, and long term components with time constants of 1 minute, 17 hours, and 8 days, respectively. Removal of the short term autoregulation component resulted in better agreement with the data in all cases as shown in Figure 4-15. It appears that further investigation into the autoregulation segments of the long term model will be required. It is not known whether this model has previously been validated for such short term simulations. It is interesting to note, however, that the removal of all except the long term autoregulatory components results in almost identical values for all simulated variables at the end of 28 days, including peripheral resistance; however, the major transient changes were 90% completed after 2-1/2 days rather than 24 hours. All other simulations were performed with the autoregulation intact.

Long term hemodynamic changes are compared with several bed rest results from studies of from 2 to 7 weeks in Figure 4-16. While agreement between model and data is generally good, variation of data among all the studies is very wide and not necessarily related to length of bed rest.

The pattern of initial decrease preceding an increase in plasma concentrations of aldosterone and angiotension predicted by the model is supported by data from the literature in Figure 4-17. (As far as is known, this represents the only data for prolonged effects on renin and aldosterone that is available; no angiotension data was located). Since

renin is a precursor to angiotension, it is reasonable to compare the renin data with the angiotension simulation. It is shown that the model has been able to reconcile seemingly conflicting data which show both increases and decreases in certain hormones as a result of reduced gravity effects.

The increase, rather than decrease, in ADH during the first day of simulation appears to be contradictory to the belief of many reviewers of bed rest studies, (i. e., McCally and Graveline, 1963; Piemme, 1968). It is interesting to note, however, that no data could be located that conclusively demonstrate that ADH is below control levels after an hour of immersion or bed rest. A recent review on ADH control concludes that while ADH may decrease temporarily during postural changes due to changes in atrial pressure, this effect does not appear to be long lasting (Goetz, et al, 1975). Furthermore, primary control of ADH appears to lie in the hypothalamic osmolarity receptors rather than atrial volume receptors. The long term model contains both osmo- and volume- control of ADH, but there is an adaptive effect included in the atrial pressure feedback loop.

Data on the body fluid volume changes during 28 days of bed rest are presented in Figure 4-18. Agreement with the simulation of these variables is good except for the more dramatic hemoconcentration of the model (see Figure 4-14(d). This difference is due to two factors: a) the study cited in this data utilized frequent blood draws which diminished red cell volume; this was not accounted for in the simulation, and b) this and other experimental studies strongly suggest a diminution of red cell mass due to inhibition or cessation of red cell mass production; the simulation did not predict significant changes in red cell mass. A prior systems analysis on the erythropoiesis system, conducted as a part of this program, has resulted in an improved red cell production subsystem (TIR 741-MED-4012) model which could easily be incorporated into the long term model and more accurately predict the changes observed in red cell mass.

Figure 4-19 shows some experimentally determined changes in renal function during bed rest. Comparison of changes in urine and

sodium excretion with the simulation results (Figure 4-15(b) indicates reasonably good agreement. The simulated renal blood flows and GFR compares well with the experimental exercise group, but not the control non-exercisers.

The results of the short term simulation of 70° tilt and supine exercise preceding and following the bed rest simulation are shown in Figures 4-20 and 4-21. All results are shown as changes from the supine position immediately preceding the stress. Also shown are changes in supine values as a result of bed rest. Agreement with the supine exercise data is better than agreement with tilt data. This was not an unexpected result in view of the extremely simple hypothesis that was employed to differentiate pre-bed rest and post-bed rest conditions in the model. Only total blood volume changes, certain vascular resistances and local cardioacceleration changes were used in the short term subsystems to distinguish pre- and post-bed rest physiological states. These changes were obtained from the long term simulation, but other changes that were observed at the end of long term bed rest were not included - such as hormonal changes, unstressed volume changes, pulmonary resistance, blood viscosity effects, etc. Also, since the long term model does not contain a leg compartment, it was not possible to simulate suspected changes that occurred in the extremity vasculature such as "drying up of the legs", reverse stress relaxation, and compliance changes. These latter effects, if included, would have affected the tilt simulation more than supine exercise, since in supine exercise, pooling of blood in the legs does not occur, while in tilt, bed rest induced changes in vessel capacity and tone would have marked effects on blood pooling and hence, cardiac performance. In addition, experimental data obtained during tilt is highly time-dependent, particularly if excess pooling or extravasation of fluid occurs. This can be seen in Figure 4-20 where experimental values at the five-minute mark are shown for all variables except for heart rate where the dotted lines indicate 1 minute values as well. If this time-dependency is related to tissue filtration effects, then it might be expected that agreement with

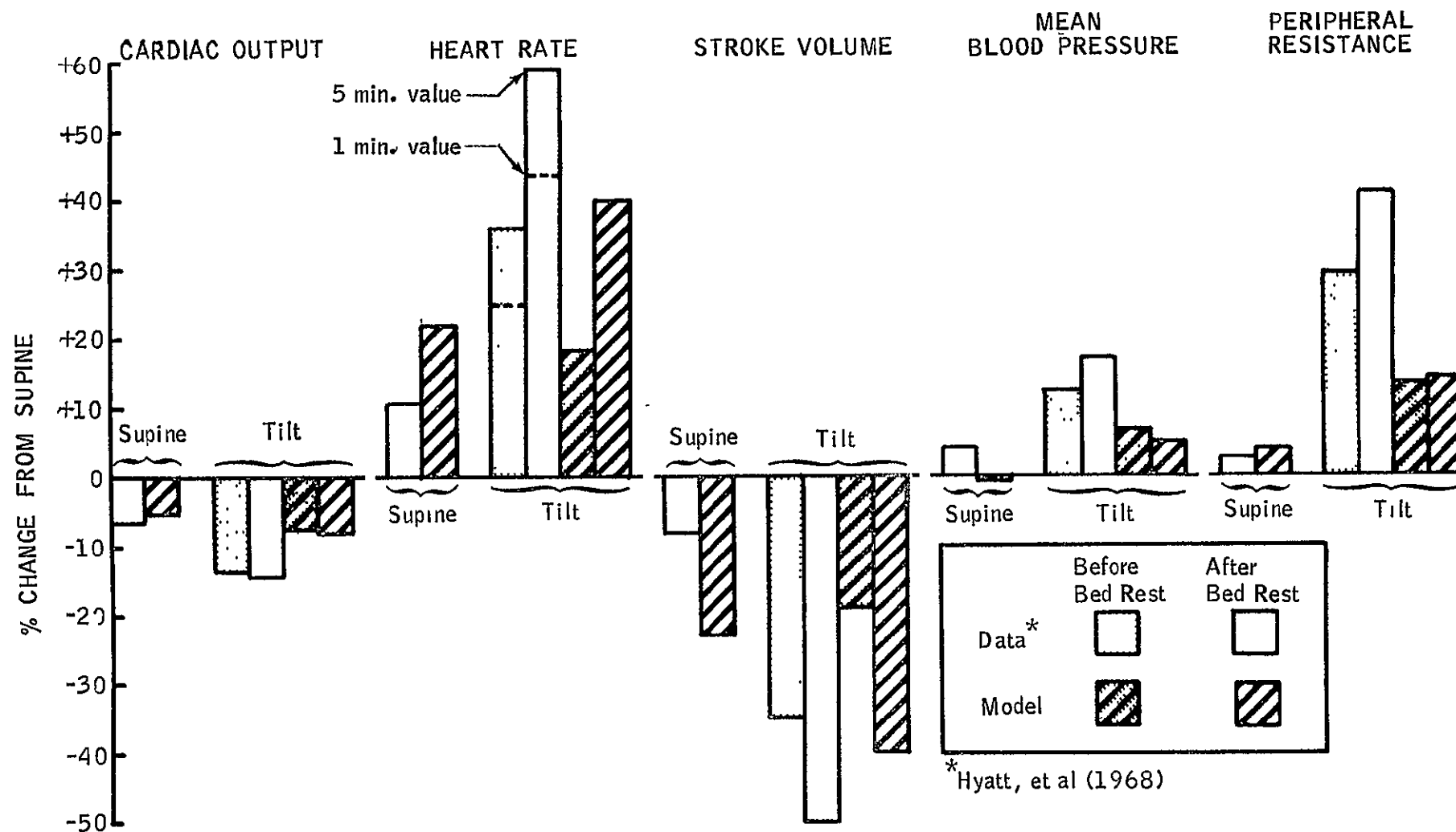


FIGURE 4-20 RESPONSE TO 70° TILT FROM SUPINE: BEFORE AND AFTER BED REST
COMPARISON OF DATA AND MODEL

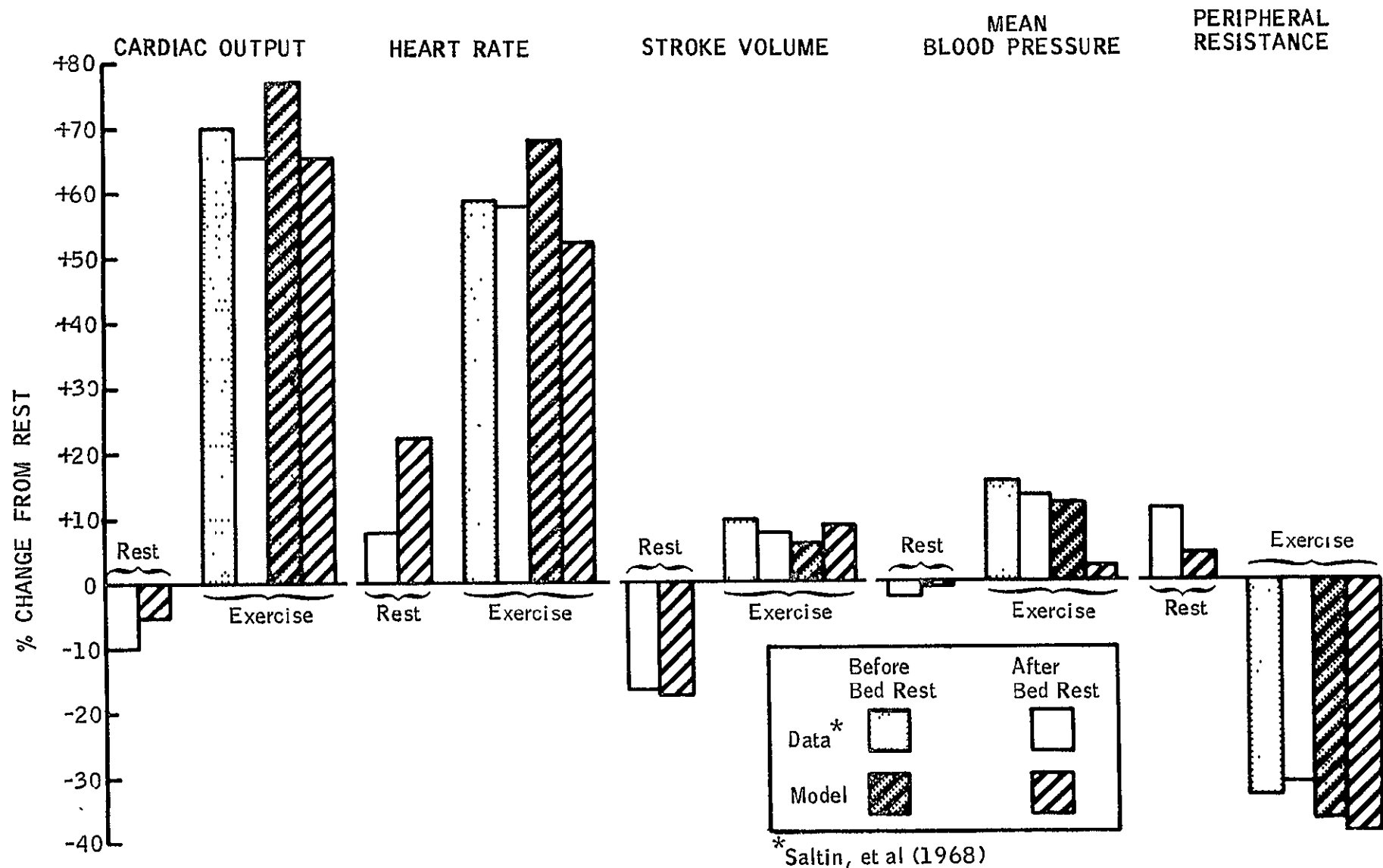


FIGURE 4-21 RESPONSE TO 50 WATT SUPINE EXERCISE: BEFORE AND AFTER BED REST
COMPARISON OF DATA AND MODEL

data would be poorer after prolonged tilting since the short term models do not account for this effect. This observation suggests the need for either obtaining data immediately after tilting and/or improving the short term subsystem models by accounting for transcapillary filtration, especially in the leg compartments. Accounting for other suspected changes due to bed rest would not only improve the agreement between data and model for these post-bed rest stresses, but also help quantify the relative significance of these changes. The potential application of this approach of hypothesis testing with simulation models has already been demonstrated in a previous phase of this project (TIR-741-MED-4009).

In summary, this preliminary attempt to simulate bed rest and post-bed rest stress has demonstrated the capability of the whole-body algorithm to perform a sequential series of short and long term stresses automatically and somewhat accurately. No major structural changes in any subsystem model was necessary to accomplish this simulation attesting to the basic soundness of the original models and to the correctness of approach in designing and implementing the whole-body algorithm. Certain aspects of model behavior have suggested that further analysis and perhaps structural modification is needed to improve the simulation in certain critical areas: erythropoiesis, autoregulation, stress relaxation, ADH regulation, inclusion of a leg compartment in the long term model, and inclusion of an extravascular compartment in the short term models. In addition, the model as presently designed is suitable for testing the effects of many suspected mechanisms that are believed to underly some of the unexplained observations. Further simulation studies may also help to distinguish the effects of a reduced gravity factor from the reduced activity factor, both of which accompany bed rest.

5.0 CONCLUSIONS AND RECOMMENDATIONS

The whole-body algorithm in its current state as described and verified in this report does meet or exceed all the stated objectives and design requirements as set forth in the NAS9-12932 contract, Program Plan, and Design Specification. The foregoing sections support and demonstrate this conclusion. The value of systems analysis and the selected design approach for developing a whole-body algorithm is demonstrated and confirmed by the successful accomplishment of this vast undertaking within the cost and schedule constraints of the contract.

A very important finding in this study is that the selected design approach, which is consistent with sound systems analysis procedures, described in this report has provided a whole-body algorithm simulation model that not only meets the objectives and requirements but also:

- 1) provides a flexible structure for making changes in the model without total disruption of the entire system.
- 2) provides a central repository for collecting individual and total system hypotheses for physiological changes due to the space flight environment.
- 3) provides a simulation model which is capable of testing multiple system interaction and total system hypotheses related to any of the stresses for which it is designed to simulate.
- 4) provides the basic capability to simulate multiple and sequential stresses with little or no basic change to the model.
- 5) provides the basic structure for adding new subsystem models, improved sections in the subsystem models, and the mechanisms and/or interface changes necessary to simulate additional stresses including pathophysiological stresses.

The whole-body algorithm simulates each of the stresses of interest at least as well as does each of the subsystem models, for which they were designed to simulate, in a stand-alone mode. This is significant because each of the subsystem models were not designed to simulate

many of the stresses for which the others were designed. This is, however, not surprising since the interfacing models provide each other with better representations of their interfacing subsystems than was represented in the stand-alone model. In many cases the interfacing subsystems were represented in each of the stand-alone models in an entirely artificial or at least very crude manner. It has been shown that joining complex subsystem models into an integrated larger scale model can be successfully accomplished, not only from an operational and mechanical standpoint, but in a manner that results in a superior representation of the physiological system. The response of the whole-body algorithm to bicycle ergometry exercise should, at least from a total system viewpoint, be among the best simulations in existence since all three of the short term subsystem models were originally designed to simulate the response of that subsystem to bicycle ergometry.

A wide variety and large number of stresses as well as different stress levels have been simulated including environmental disturbances (ambient temperature changes, hypoxic and hypercapnic gas mixtures), metabolic changes (supine and sitting exercise), and special experimental situations (tilt-table studies, LBNP, and bed rest). Simulation of short term stresses resulted in simultaneous and integrated responses from the cardiovascular, respiratory, and thermoregulatory subsystems and the accuracy of a large number of responding variables was verified. The capability of simulating significantly longer responses was demonstrated by validating a four week bed rest study. In this case, the long term subsystem model was found to reproduce many experimentally observed changes in circulatory dynamics, body fluid-electrolyte regulation and renal function.

In addition to testing separate short and long term stress responses, the versatility of the whole-body algorithm was illustrated by its ability to combine these stresses and automatically sequence between the long and short term model subsystems. This severe challenge to the operating characteristics of the model was provided by a simulation of bed rest preceded and followed by tilt and exercise stress tests. The potential

usefulness of the model for testing hypotheses during bed rest (and by analogy, weightless space flight) was illustrated. While the emphasis of validation was placed on steady-state results, the transient characteristics of both long and short term responses was demonstrated as well. It was also found that suitable challenges to a model as detailed and integrated as the whole-body algorithm requires a physiological data base which is as equally detailed and integrated. Much of this information was found to be lacking. It is interesting to note that some of the most valuable data for validating the whole-body algorithm came from laboratories engaged in both physiological research and modeling. This project has, therefore, provided additional support for advocating a continuing research program concerned with measuring whole-body responses to environmental and metabolic disturbances and it has demonstrated the capability of combining complex subsystem models for integrating this diversity of physiological information.

Perhaps one of the most important conclusions which has been reached in this study is that the selected approach has yielded a whole-body algorithm simulation model which is extremely stable. This is true not only from the standpoint of response to stimuli or input conditions, but also from the operational viewpoint. The model seems to respond with reasonably good results even when gross inaccuracies or inadequacies were present during the development phase. Guyton has made similar observations concerning his model and attributes this phenomena to the extreme stability of the real system. Perhaps this observation confirms the idea that interacting subsystem models better represents the overall regulatory capability of the real system, and, therefore, inherits some of its innate stability and compensatory characteristics.

Even though this first version of the whole-body algorithm is an initial attempt to develop a total body system model, it provides a very powerful research tool and may be found to have many and varied practical applications as well. This program has been directed toward its development and verification for the specific purposes for which it was designed and, therefore, does not address the many possibilities

for important applications. For that matter, applications of the model for which it was designed are not included in this program. Although a great deal was learned in the design and development of the whole-body algorithm, the next step is most certainly to put this powerful tool to use.

While the whole-body algorithm has reached the end of this first phase of development and already has very significant simulation capabilities, this is not to say that the work in this area is complete. Quite the contrary; the first version of the whole-body algorithm is only a start toward developing a total body simulation system. Many subsystems have yet to be represented, particularly in the biochemical and neurological areas. Many improved mechanisms in the existing subsystems are being developed by other investigators and should be included. Many other experimental stresses and verified physiological hypotheses should be represented in the model.

Many specific recommendations for improvements, additions, and more validation have been formed during the development of the first version of the whole-body algorithm. The more important ones are:

- 1) Add new compartmentization in the long term model to represent the legs since many of the important long term changes occurring in zero-g and bed rest involve the legs.
- 2) Add the capability to simulate postural changes in 1-g to the long term model for better simulation of the postflight readaptation to 1-g.
- 3) Improve and integrate the autonomic control system for both the cardiovascular and respiratory subsystems. This is particularly needed for central and local integrated autonomic control for all stresses with the same formulation or representation. Better discrimination between sympathetic and parasympathetic control, lung stretch receptor reflex, autonomic control effecting catecholamine release from the adrenal medulla, different representation of similar controllers in each subsystem, and resetting or sensitivity changes in receptors and control centers are other areas which need investigation.

- 4) Improve definition of the long term - short term interface or improvements in the cardiovascular subsystem are needed to better simulate the gray area between short term and long term changes (particularly around one hour of simulated time). This is particularly needed to simulate the plasma filtration, stress relaxation changes, autoregulation, and many hormonal changes which do occur following many short term stresses (such as head-up tilt in 1-g) and are needed to produce the transient response to the system for the next hour or so.
- 5) Improve representation and/or validation of long term adaptation/acclimatization (particularly since this is an area of interest in space flight) to long term stress. Data from people living in hot and cold climates and at high altitudes may provide a starting place for such study.
- 6) Improve respiratory - thermoregulatory subsystem interface (other than through the cardiovascular subsystem) to improve simulation of respiratory heat losses and thermal influences on respiratory control.
- 7) Improve the flexibility for simulating different population responses to stress such as the effect of training/conditioning, age, etc.
- 8) Continue validation particularly in the areas of transient responses (both on and off) such as to exercise and thermal stress and multiple stresses for which data are available such as exercise and environmental stress, dehydration and exercise, tilt and environmental stress, and combined environmental stresses. More testing of bed rest hypotheses is also needed.

It appears from the foregoing that this development of a whole-body algorithm is not complete and probably never will be complete. It is, however, a very good beginning and this study has not only produced a very useful tool, but has pointed the way for future work in this area.

REFERENCES

- Abramson, D. I., *Circulation in the Extremities*, Academic Press, New York, 1967.
- Albergoni, V., C. Cobelli, G. Torresin, "Interaction Model between the Circulatory and Respiratory Systems", IEEE Transactions on Biomedical Engineering, Vol. 19, 1972, pp. 108-113.
- Arborelius, M., Jr., U. I. Balldin, B. Lilja and C.E.G. Lundgren, Hemodynamic Changes in Man During Immersion with the Head Above Water, Aerospace Medicine, Vol. 43, 1972, pp. 592-598.
- Astrand, P. O. and K. Rodahl, *Textbook of Work Physiology*, McGraw-Hill Book Company, New York, 1970.
- Atkins, A., D. Mitchell, "Simulating the Thermal Response of A Working Man with a Computer", International Journal of Biometeor, Vol. 15, 1971, pp. 183-188.
- Bartok, S. J. and L. D. Carlson, Cardiovascular Changes During Tilt and Leg Negative Pressure Tests, Aerospace Medicine, Vol. 39, 1968, pp. 1157-1162.
- Benzinger, T. H., *Heat Regulation: Homeostasis of Central Temperature in Man*, Physiological Review, 49; 1969, pp. 671-759.
- Birkhead, N. C., et al. Cardiodynamic and Metabolic Effects of Prolonged Bed Rest. AMRL-TDR-63-37, 1963.
- Blockley, W. V., Identification of a Fundamental Inadequacy in LBNP as a Circulatory Challenge in Deconditioning Assessment. In Preprints of the 1970 Annual Scientific Meeting of the Aerospace Medical Association, 1970, pp. 67-68.
- Croston, R. C., "A-Cardiovascular Control System Simulation for Exercise", Ph.D. Dissertation, University of Houston, May 1973.
- Damato, A. N., et al. Cardiovascular Response to Acute Thermal Stress (Hot Dry Environment) in Unacclimatized Normal Subjects, *American Heart Journal*, Vol. 76, 1968, pp. 769-774.
- Deitrick, J. E., G. D. Whedon, and E. Shoor, Effects of Immobilization upon Various Metabolic and Physiologic Functions of Normal Men, *American Jnl. Medicine*, Vol. 4, 1948, p. 3-36.
- Dietlein, L. F. and W. V. Judy, Experiment M-1 Cardiovascular Conditioning in Gemini Midprogram Conference. NASA SP-121, 1966, pp. 381-391.

- Dripps, R. D. and J. H. Conroe, Jr., The Effect of the Inhalation of High and Low Oxygen Concentrations on Respiration, Pulse Rate, Ballistocardiogram and Arterial Oxygen Saturation of Normal Individuals, Amer. J. Physiol., Vol. 149, 1947, pp. 277-291.
- Duffin, J., The Chemical Regulation of Ventilation, Anaesthesia, Vol. 26, 1971, pp. 142-154.
- Ekblom, B., et al. Effect of Training on Circulatory Response to Exercise, Journal Applied Physiology, Vol. 24, 1968, pp. 518-528.
- Ekelund, L. G. and A. Holmgren, Circulatory and Respiratory Adaptation During Long Term, non-Steady-State Exercise, in the Sitting Position. Acta Physiol. Scand., Vol. 62, 1964, pp. 240-255.
- Epstein, M., Studies of Sodium Homeostasis During Simulated Weightlessness: Application of the Water Immersion Model to Man, in Proceedings of the 1972 LBJ Space Center Endocrine Program Conference, C. S. Leach (Coordinator), a National Aeronautics and Space Administration Report No. TMX-58134, 1974, NASA, Washington, D. C., 20546, Section 9.
- Epstein, M. and T. Saruta, Effect of Water Immersion on Renin-Aldosterone and Renal Sodium Handling in Normal Man, Journal Applied Physiology, Vol. 31, 1971, pp. 368-374.
- Farrell, E. J. and J. H. Siegel, "Investigation of Cardio-respiratory Abnormalities Through Computer Simulation", Computers in Biomedical Research, Vol. 5, 1973, pp. 161-186.
- Fasola, A. F. and J. H. Triebwasser, The Renin Response to Lower Body Negative Pressure Stress Testing and the Effect of Exercise During Prolonged Bed Rest. In Preprints of the 1970 Annual Scientific Meeting of the Aerospace Medical Association, 1970, pp. 63-64.
- Finch, C. A. and C. Lenfant, Oxygen Transport in Man, New England Journal Medicine, Vol. 286, 1972, pp. 407-415.
- Fukui, Y., "A Study of the Human Cardiovascular-Respiratory System Using Hybrid Computer Modeling", The University of Wisconsin, Ph.D. dissertation, 1972.
- Fiijihara, Y., J. Hildebrandt, and J. R. Hildebrandt, "Cardio-respiratory Transients in Exercising Man II. Linear Models", Journal of Applied Physiology, Vol. 35, No. 1, 1973, pp. 68-76.

- Fuller, J. H., E. M. Bernauer, and W. C. Adams, Renal Function, Water and Electrolyte Exchange During Bed Rest with Daily Exercise, Aerospace Medicine, Vol. 41, 1970, pp. 60-72.
- Gauer, O. H., Body Fluid Regulation During Immersion in Hypogravic and Hypodynamic Environments, NASA SP-269, 1971, National Aeronautics and Space Administration, Washington, D. C., Section 26, pp. 345-355.
- Goetz, K. L., G. C. Bond and D. D. Bloxham, Atrial Receptors and Renal Function, Physiol. Review, Vol. 55, 1975, pp. 157-205.
- Grodins, F. S., J. Buell, and A. J. Bart, "Mathematical Analysis and Digital Simulation of the Respiratory Control System", Journal of Applied Physiology, 22, No. 3, pp. 260-276, 1967.
- Guyton, A. C., Coleman, T. G. and H. J. Granger, Circulation: Overall Regulation, Ann. Review Physiology, Vol. 34, 1972, pp. 13-46.
- Guyton, A. C., C. E. Jones, and T. G. Coleman, "Circulatory Physiology - Cardiac Output and its Regulation", 2nd Ed., W. B. Saunders Company, Philadelphia, Pa., 1973.
- Haber, E., Human Vasoregulation by Renin, Angiotension, and Aldosterone, In Proceedings of the 1970 Manned Spacecraft Center Endocrine Program Conference, 1971, NASA TMX-58068, National Aeronautics and Space Administration, Washington, D. C., 20546, Section 7.
- Hardy, J. D. and J. A. J. Stolwijk, Partitional Calorimetric Studies of Man During Exposure to Thermal Transients, Journal Applied Physiology, 21, 1966, pp. 1799-1806.
- Hatcher, J. D. and D. B. Jennings (Editors), Proceedings of the International Symposium on the Cardiovascular and Respiratory Effects of Hypoxia, Hafter Publishing Co., 1966.
- Hyatt, K. H., et al, Study of Post-Recumbency Orthostatism and Prophylactic Measures for Prevention of this Phenomenon. NASA CR-92178, Part 1 & 2, 1968.
- Hyatt, K. H., et al., A Study of the Role of Extravascular Dehydration in the Production of Cardiovascular Deconditioning by Simulated Weightlessness (Bedrest). Final Report, 1970, NASA Contract T-68099.
- Johnson, J. M., L. B. Rowell and G. L. Brengleman, Modification of the Skin Blood Flow-Body Temperature Relationship by Upright Exercise, Journal Applied Physiology, Vol. 37, 1974, pp. 880-886.

- Johnson, P. C., C. L. Fischer and C. S. Leach, Hematologic Implications of Hypodynamic States in Hypogravic and Hypodynamic Environments, NASA SP-269, National Aeronautics and Space Administration, Washington, D. C., Section 2, pp. 27-34.
- Johnston, R. S. and L. F. Dietlein (Coordinators). The Proceedings of the Skylab Life Sciences Symposium, August 27-29, 1974, National Aeronautics and Space Administration Report No. TMX-58154, Washington, D. C. 20546.
- Kontos, H. A., et al., Comparative Circulatory Responses to Systemic Hypoxia in Man and in Unanesthetized Dog, Journal Applied Physiology, Vol. 23, 1967, pp. 381-386.
- Korner, P. I., Integrative Neural Cardiovascular Control, Physiol. Review. Vol. 51, 1971, pp. 312-367.
- Lamb, L. E., Circulatory Problems in Prolonged Space Flight, in Hypodynamics and Hypogravics, M. McCally (Ed.), Academic Press, N. Y. 1968, pp. 163-179.
- Linnarsson, D., Dynamics of Pulmonary Gas Exchange and Heart Rate Changes at Start and End of Exercise, Acta Physiol. Scand., Suppl. 415, 1974, pp. 3-68.
- McCally, M., L. E. Kazarian and H. E. Von Gierke, Cardiovascular and Metabolic Effects of Bed Rest and Immobilization - Simulated Weightlessness, Proceedings of the 21st International Astronautical Congress, 1971, pp. 264-282.
- McCally, M. and D. E. Graveline, Physiologic Aspects of Prolonged Weightlessness, New England Journal Medicine, 269, 1963, pp. 508-516.
- Mitchell, J. W., J. A. J. Stolwijk, E. R. Nadel, "Model Simulation of Blood Flow and Oxygen Uptake During Exercise", Biophysical Journal, Vol. 12, 1972, pp. 1452-1466.
- Murray, R. H. and M. McCally (eds.), Proceedings of the Symposium on Hypogravic and Hypodynamic Environments, French Lick, Ind., NASA SP-269, National Aeronautics and Space Administration, Washington, D. C., 1971.
- Murray, R. H., et al., Hemodynamic Effects of Graded Hypovolemia and Vaso-depressor Syncope Induced by Lower Body Negative Pressure, American Heart Journal, Vol. 76, 1968, pp. 799-811.
- Murray, R. H., et al, Hemodynamic Effects of Hypovolemia in Normal Subjects and Patients with Congestive Heart Failure, Circulation, Vol. 39, 1969, pp. 55-69.

- Musgrave, F. S., F. W. Zechman and R. C. Mains, Comparison of the Effects of 70° Tilt and Several Levels of Lower Body Negative Pressure on Heart Rate and Blood Pressure in Man, Aerospace Medicine, Vol. 42, 1971, pp. 1065-1069, and Changes in Total Leg Volume During Lower Body Negative Pressure, Aerospace Medicine, Vol. 40, 1969, pp. 602-606.
- Piemme, T. E., Body Fluid Volume and Renal Relationships to Gravity, in Hypodynamics and Hypogravics, M. McCally (Ed.), Academic Press, N. Y., 1968, pp. 133-161.
- Reynolds, W. J. and H. R. Milhorn. Transient Ventilatory Response to Hypoxia With and Without Controlled Alveolar $p\text{CO}_2$, Journal Applied Physiology, V. 35, 1973, pp. 187-196.
- Reynolds, W. J., H. T. Milhorn and G. H. Holloman, Jr., Transient Ventilatory Response to Graded Hypercapnia in Man, Journal Applied Physiology, Vol. 33, 1972, pp. 47-54.
- Richardson, D.W., A. J. Wasserman and J. L. Patterson, Jr., General and Regional Circulatory Responses to Change in Blood pH and Carbon Dioxide Tension, Journal Clinical Invest., Vol. 40, 1961, pp. 31-43.
- Rowell, L. B., The Cutaneous Circulation, in Physiology and Biophysics, T.C. Ruch, H. D. Patton and A. M. Scher (Ed.), W.B. Saunders Co., Philadelphia, 1974, Chapter 12, pp. 185-199.
- Rowell, L. B., et al., Redistribution of Blood Flow During Sustained High Skin Temperature in Resting Man, Journal Applied Physiology, Vol. 28, 1970, pp. 415-420.
- Rowell, L. B., G. L. Brengelmann and J. A. Murray. Cardiovascular Responses to Sustained High Skin Temperature in Resting Man, Journal Applied Physiology, Vol. 27, 1969, pp. 673-680.
- Sagawa, K., Overall Circulatory Regulation, Annual Review Physiology, Vol. 31, 1969, pp. 300-328.
- Saltin, B., et al., Response to Exercise After Bed Rest and After Training: A Longitudinal Study of Adaptive Changes in Oxygen Transport and Body Composition, Circulation, Vol. 38, 1968, pp. VII-1 - VII-78.
- Saltin, B., A.P. Gagge and J.A.J. Stolwijk, Body Temperatures and Sweating During Thermal Transients Caused by Exercise, Journal Applied Physiology, 28, 1970, pp. 318-327.
- Saxton, C., Respiration During Heat Stress, Aviation Space Environ. Medicine, Vol. 46, 1975, pp. 41-46.

- Scher, A. M. , Control of Arterial Blood Pressure, in Physiology and Biophysics, T. C. Ruch, H.D. Patton and A.M. Scher (Ed.), W. B. Saunders Company, Philadelphia, 1974, Chapter 10, pp. 146-169.
- Segel, N. , R. Dougherty, and M. A. Sackner, Effects of Tilting on Pulmonary Capillary Blood Flow in Normal Man, Journal Applied Physiology, Vol. 35, 1973, pp. 244-249.
- Selkurt, E.E. (Ed.), Physiology, 3rd Ed., Little, Brown, and Company, Boston, 1971.
- Shepherd, J. T. , Physiology of the Circulation in Human Limbs, in Health and Disease, W. B. Saunders Co., Philadelphia, 1963.
- Sjostrand, T. , Volume and Distribution of Blood and Their Significance in Regulating the Circulation, Physiol. Review, 33, 1953, pp. 202-228.
- Smith, P.E. , E. W. James, "Human Response to Heat Stress", Archives of Environmental Health, Vol. 9, 1964, pp. 323-342.
- Stegemann, J. , et al. , Effects of a Multi-Hour Immersion with Intermittent Exercise on Urinary Excretion and Tilt Table Tolerance in Athletes and Nonathletes. Aviation Space Environ. Medicine, Vol. 46, 1975, pp. 26-29.
- Stevens, P. M. , et al. , Influence of Long Term Lower Body Negative Pressure on the Circulatory Function of Man During Prolonged Bed Rest. , Aerospace Medicine, Vol. 37, 1966, pp. 357-367.
- Stolwijk, J.A.J. , "Mathematical Model of Thermoregulation", Physiological and Behavioral Temperature Regulation (ed. by J.D. Hardy, A. P. Gagge and J.A.J. Stolwijk), Charles C. Thomas, Springfield, Ill., 1970.
- Stolwijk, J.A.J. and J. D. Hardy. , Partitional Calorimetric Studies of Responses of Man to Thermal Transients, Journal Applied Physiology, 21, 1966, pp. 967-977.
- Taylor, H. L. , et al. , Effects of Bed Rest on Cardiovascular Function and Work Performance, Journal Appl. Physiology, Vol. 2, 1949, pp. 223-239.
- Tuckman, J. and J. Shillingfor, Effect of Different Degrees of Tilt on Cardiac Output, Heart Rate, and Blood Pressure in Normal Man, British Heart Journal, Vol. 28, 1966, pp. 32-39.
- Thauer, R. , Circulatory Adjustments to Climatic Requirements, in Handbook of Physiology. Circulation. Washington, D.C., Amer. Physiol. Soc., 1962, Section 2, Vol. II, Chapter 55, pp. 1921-1966.

- Rushmer, R. F., Effects of Posture, in Cardiovascular Dynamics, 2nd Edition, Philadelphia: Saunders, 1961, Chapter 7.
- Vallbona, C., et al., The Effect of Bed Rest on Various Parameters of Physiological Function., Part VIII. The Effect on the Cardiovascular Tolerance to Passive Tilt. NASA CR-178, 1965.
- Vogt, F. B. and P. C. Johnson., Plasma Volume and Extracellular Fluid Volume Change Associated with 10 Days Bed Recumbency, Aerospace Medicine, Vol. 38, 1967, pp. 21-25.
- Walters, R. F., N. C. Miller, "HPMOD: A Predictive Model of Human Performance", Proceedings of 26th ACEMB, 1973, 6, pp. 11-62.
- Walters, R. F., N. C. Miller, "Interactive Modeling as a Forcing Function for Research in the Physiology of Human Performance", Simulation, 1974, pp. 1-13.
- Weissman, M. H., "Respiratory-Thermal Modeling", Research Report, Biomedical Research Division, Environmental Physiology Branch, NASA-JSC, 1971.
- Wenger, C. B., et al., Forearm Blood Flow During Body Temperature Transients Produced by Leg Exercise, Journal Applied Physiology, 38, 1975, pp. 58-63.
- Whipp, B. J. K. Wasserman, "Oxygen Uptake Kinetics for Various Intensities of Constant-Load Work", Journal of Applied Physiology, Vol. 33, No. 3, 1972.
- Wissler, E. H., "Mathematical Simulation of the Human Circulatory, Respiratory, and Thermal Systems in Exercise", 26th ACEMB, 1973, 8, pp. 4-75.
- Wolthuis, R. A., S. A. Bergman, and A. Nicogossian., Physiological Effects of Locally Applied Reduced Pressure in Man, Physiol. Review, Vol. 54, 1974, pp. 566-595.
- Wolthuis, R. A., G. W. Hoffler and R. L. Johnson, Lower Body Negative Pressure Stress, Aviation Space Environ. Med., Vol. 46, 1975, pp. 697-702.
- Womack, B. F., J. H. Hinderer, "Modeling the Effect of Respiration on Heart Rate Through Analog and Digital Computer Studies", Association for the Advancement of Medical Instrumentation Journal, Vol. 5, 1971, pp. 38-43.
- Wyss, C. R., G. L. Brengelmann, et al., Control of Skin Blood Flow, Sweating and Heart Rate: Role of Skin vs. Core Temperature, Journal Applied Physiology, Vol. 36, 1974, pp. 726-733.